

# Brazilian Multicenter Study on Efficacy and Tolerability of Trandolapril in Mild-to-Moderate Essential Arterial Hypertension. EMBATHE Substudy with Ambulatory Blood Pressure Monitoring

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**Objective** - A double-blind, placebo-controlled multicenter study involving 34 centers from different Brazilian regions was performed to evaluate the antihypertensive efficacy and tolerability of trandolapril, an angiotensin I converting enzyme inhibitor, in the treatment of mild-to-moderate systemic arterial hypertension.

**Methods** - Of 262 patients enrolled in this study, 127 were treated with trandolapril 2 mg/day for 8 consecutive weeks, and the remaining 135 patients received placebo for the same period of time. Reduction in blood pressure (BP) and the occurrence of adverse events during this period were evaluated in both groups.

**Results** - Significant reductions in both systolic and diastolic pressures were observed in patients treated with trandolapril when compared with those on placebo. Antihypertensive efficacy was achieved in 57.5% of the patients on trandolapril and in 42% of these normal values of BP were obtained. The efficacy of trandolapril was similar in all centers, regardless of the area of the country. In a subset of 30 patients who underwent ABPM, responders showed a significant hypotensive effect to trandolapril throughout the 24 hour day. The adverse event profile was similar in both trandolapril and placebo groups.

**Conclusion** - Our results demonstrate, for the first time in a large group of hypertensive patients from different regions in Brazil, good efficacy and tolerability of trandolapril during treatment of mild-to-moderate essential systemic hypertension.

**Keywords:** mild-to-moderate hypertension, trandolapril, ACE inhibitor

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Trandolapril, a nonsulfidrylic compound, is one of the newest members of the angiotensin I converting enzyme inhibitor (ACEI) class. It is a prodrug and must be hydrolysed to its active metabolite, trandolaprilate, to exert its antihypertensive effect. One important characteristic of this drug is its long-lasting biphasic half-life, ranging from 16 to 24 hours<sup>1</sup>, allowing a single dose therapy regimen.

The antihypertensive effect of trandolapril is obtained with doses varying from 1.0mg to 8.0mg/day. Even with relatively low doses such as 2.0mg/day, normalization or satisfactory blood pressure reduction e.g. a 10mmHg reduction in BP occurs in about 70% of patients, as demonstrated by many studies with distinct follow-up periods<sup>2,3</sup>.

Furthermore, the antihypertensive efficacy of this drug over placebo<sup>2,4</sup> and similar to that of many other antihypertensive compounds<sup>5</sup> has been clearly demonstrated by several studies.

Another important issue, considering that this drug, as with many other ACE inhibitors, is given once a day, is to ensure that blood pressure control is maintained throughout the 24 hour day.

The importance of the ambulatory blood pressure monitoring (ABPM) in the evaluation of blood pressure response to drug therapy is well known, especially in studying the effects of newer drugs in hypertensive patients.

Thus, the purpose of this study was to twofold: to evaluate in a multicenter trial patients with mild-to-moderate essential hypertension for tolerability to trandolapril and the antihypertensive efficacy of trandolapril in comparison with placebo as demonstrated by the reduction in office blood pressure (study 1); and to evaluate in a subgroup of patients, in a noncomparative manner, the duration of the hypotensive effect of trandolapril using the ambulatory blood pressure monitoring (ABPM) (study 2).

## Methods

**Study 1** - This study included 262 patients with mild-

to-moderate essential hypertension (102 male and 160 female), age >25 years, from 34 different medical centers.

Exclusion criteria were presence of secondary forms of hypertension, body mass index (BMI) >30kg/m<sup>2</sup>, serum creatinin levels >1.5mg/dL, serum potassium levels >5.5 mEq, and the presence of left ventricular hypertrophy in the EKG. Patients with end-organ damage and/or clinical complications due to the hypertensive state were also not admitted to the study. Women of childbearing potential not using medically acceptable contraceptive methods, and patients with systolic blood pressure levels >200mmHg or diastolic levels over 115mmHg were also excluded from this study.

The design of this study was randomized, double-blind and placebo controlled. We enrolled patients who had in the initial visit, diastolic blood pressure (DBP) levels ranging from 95 to 115mmHg after undergoing a washout period of two weeks with administration of placebo pills once a day. Following that period, patients were randomized into either a placebo (n=135) or trandolapril (n = 127) 2.0mg regimen once a day for eight consecutive weeks. In addition to blood pressure evaluation, serum creatinine and potassium levels were also determined at the beginning of the randomization period and at the end of the study.

**Study 2** – In this study 30 patients with mild-to-moderate essential hypertension from three different centers, 24 female and 6 male, age >18 years were included. Inclusion and exclusion criteria were the same as for study 1.

This open-label study enrolled patients with DBP varying from 95 to 115mmHg, in the initial visit. After a two-week washout period, trandolapril 2.0mg per day was administered during 12 consecutive weeks. Blood pressure readings were obtained during each visit to the clinic and at the end of washout (week 0) and trandolapril treatment (week 12) periods. All patients of this study had their blood pressure evaluated by ambulatory blood pressure monitoring (ABPM).

In both studies the following data were obtained at the initial visit: duration of the hypertension, smoking, drinking, physical activity habits, previous use of antihypertensive drugs and the presence of concomitant diseases. At each visit to the clinic during the follow-up period, office blood pressure levels, body weight and heart rate (HR) of all patients were monitored, and a complete physical examination was also performed. Severity and duration of adverse events related to the investigational drug were also recorded at each visit.

For both studies, office blood pressure levels represent the mean of 3 consecutive readings using a mercury sphygmomanometer and performed by the same investigator after 5m at rest in a quiet environment, with the patient in a sitting position. Phases I and V of Korotkoff sounds were used for systolic (SBP) and diastolic (DBP) measurements.

Blood pressure control was defined when office blood pressure during treatment was lower than 140/90mmHg. If a

DBP reduction of 10mmHg compared with baseline was achieved, despite not reaching normal levels, patients were defined as responders.

In study 2, ABPM was performed with a Spacelabs monitor, model 90207, recording blood pressure levels every 15m in the vigil period and every 20m in the sleep period. The time of the day for beginning ABPM varied from patient to patient; the vigil period included patient's regular activities (job, study, home care, meals, etc.) and the sleep period was considered that from the time patients went to bed to the hour of getting up the following morning. For data analyses only those ABPM records showing BP of at least 80% were accepted.

Both studies were approved by local Ethics Committees and before study initiation an informed consent was signed by each patient.

## Results

**Study 1** – Table I shows the demographic characteristics of the study groups. There was a homogeneous patient distribution in the placebo and trandolapril groups and no statistically significant difference was observed between the two groups for all demographic parameters evaluated.

Before study initiation, in the placebo group, 64 patients used one drug and 47 used two or more drugs. Similarly, in the group treated with trandolapril, 55 used one drug before starting the study and 46 used two or more drugs. The most frequent concomitant diseases present in both groups were: diabetes mellitus, obesity, dyslipidemia, asthma and varicous veins.

There were no significant changes in clinical examination, body weight and HR alterations during the eight week observation period (table II).

Serum creatinine levels were not different between the two groups not only during the basal period (0.9±0.2 vs 0.9±0.22mg/dL, ns; placebo vs trandolapril group, respectively) but also at the end of the study, 0.9±0.2mg/dL levels for placebo group, and 0.87±0.2mg/dL, for trandolapril group (ns). On the other hand, serum potassium levels that were similar in the initial evaluation (4.2±0.4 vs 4.2±0.4mEq/L; placebo and trandolapril, respectively) become slightly greater at the end of treatment in the trandolapril group (4.3±0.4 vs 4.2±0.4mEq/L, p<0.05).

Figures 1 and 2 show SBP and DBP values, respectively, in both groups before and during therapy. At the end of the washout period (placebo), the two groups showed similar pressure values both for SBP (156.1±18 vs 157.3 ± 15mmHg, ns) and for DBP (100.3±6.6 vs 101±6.3mmHg, ns). It was observed that both treatments determined gradual BP reduction during the eight week evaluation period; this effect was significantly greater with trandolapril when compared with the placebo group. Thus, BP levels, both SBP and DBP recorded at the end of the study were significantly lower in the trandolapril group (143 ± 18/91 ± 9.8 mmHg), when compared with the placebo group (149 ± 19/94 ± 10.4mmHg, p<0.05).

**Table I – Demographic characteristics of patients in placebo and trandolapril group (study 1) and trandolapril evaluated with AMBP (study 2)**

	Study 1		Study 2
	Placebo (n=135)	Trandolapril (n=127)	Trandolapril (n=30)
Age (years)	53.1±11.3	53.0±11.6	56.3±10.7
Gender (M/F)	55/80	47/80	6/24
Ethnic group			
White	64	71	12
Non white	58	50	16
Non referred	13	6	2
Smoking Y/N	24/111	9/118	2/28
Drinking Y/N	15/120	9/118	1/29
Physical activity			
Y/N	49/86	49/78	12/18
History time (years)	9.4±8.2	8.7±8.3	11±7
Hypertension type			
Mild/moderate	72/62	67/60	23/7
Non specified	1	-	-
Previous drugs Y/N	111/24	101/26	25/5
Concomitant diseases			
Y/N	41/94	39/88	13/17

In addition, we observed that BP control (42% vs 27%,  $p<0.05$ ) and responder rates (16% vs 11%) were significantly greater in the trandolapril group when compared with the placebo group. Therefore, antihypertensive efficacy was significantly greater in the trandolapril group when compared with the placebo group (57.5% vs 37.8%,  $p=0.002$ ).

Regarding the presence of side effects, the most prevalent adverse event in the placebo group was headache (17%), and in the trandolapril group was cough (10%). Other frequent adverse events in the placebo group were dizziness (6%), cough (4%), palpitations (4%) and weakness (3%). In the trandolapril group headache (7%) and dizziness (5%) were also reported.

Twelve patients from the placebo group and four from the trandolapril group did not complete the study or were considered lost in the follow-up.

**Study 2** – Table I shows the characteristics of this group of patients. We can observe that patients of this study were very similar to those of study 1.

In this study, 13 patients had been using one drug and the others had been using two or more drugs to previously treat their hypertension. Diabetes mellitus, osteoarticular diseases, hypothyroidism and varicous veins were the most common concomitant diseases present in this group.

As in study 1, baseline and end-study levels of serum creatinine were similar ( $0.87\pm0.2$  vs  $0.9\pm0.25$ mg/dL). In this study, plasmatic potassium levels were similar in placebo and trandolapril groups  $4.5\pm0.45$  and  $4.5\pm0.52$ mEq/L). Baseline and end-study body weight ( $65.7\pm15.3$  vs  $67.3\pm10.8$ kg) and heart rate ( $75.4\pm11.1$  vs  $73.9\pm9.8$  bpm) were also not different.

Headache was the most frequent side effect (4 cases) while only one patient had a cough complaint.

As in study 1 we observed in study 2 a statistically significant reduction in pressure levels after 12 weeks of treatment with trandolapril. Both ambulatory SBP and DBP values were significantly reduced with trandolapril ( $161\pm12/102.5\pm5.5$  vs  $149\pm14.3/93.6\pm7.9$ mmHg,  $p<0.05$ , basal and final, respectively). We also observed antihypertensive efficacy rates, that is normalization and/or reduction of at least 10mmHg of BP levels, similar to those obtained in study 1.

Figures 3 and 4 represent the hourly averages of SBP and DBP, respectively, obtained from ABPM of patients considered responders to trandolapril at office BP records. It was observed that trandolapril treatment brought about significant reduction in BP, which were maintained 24h a day, especially for SBP. The hypotensive effect was slightly greater in the vigil period when compared with the sleeping period.

## Discussion

Results obtained in both studies show that trandolapril offers a satisfactory approach for BP reduction.

Our observations are in accordance with previous noncomparative studies reporting SBP reduction from 6 to 15% and 8 to 17% for DBP<sup>6,7</sup>. The efficacy of blood pressure reduction in these studies was related to the observation period. In studies in which duration of follow up was up to 12 months, the observed reductions reached 19% for SBP, while for DBP no further reductions were observed<sup>6</sup>.

In our studies, we observed that for both the 12 week (three months) and the eight week (two months) observation periods, BP reductions for the trandolapril group were 7.5% and 9% for SBP, and 8.2% and 10% in DBP, supporting previous data in the literature.

Regarding the population characteristics, the drug profile was adequate. This was a multicenter study, with intake food patterns (salt ingestion) and ethnic charac-

**Table II – Body weight and heart rate in placebo (n=135) and trandolapril group (n=127)**

Week/Group	-2	0	2	5	8
Weight (kg)					
Placebo	68.9±9.9	69.0±9.80	69.2±9.9	69.1±10.2	69.0±10.2
Trandolapril	68.0±10.8	68.1±10.7	67.9±10.7	67.7±10.8	67.5±10.9
Heart rate (bpm)					
Placebo	75.1±9.5	75.7±9.85	76.3±9.7	76.6±10.4	76.4±9.3
Trandolapril	76.1±9.48	75.6±9.11	76.4±8.8	75.4±8.7	75.5±8.2

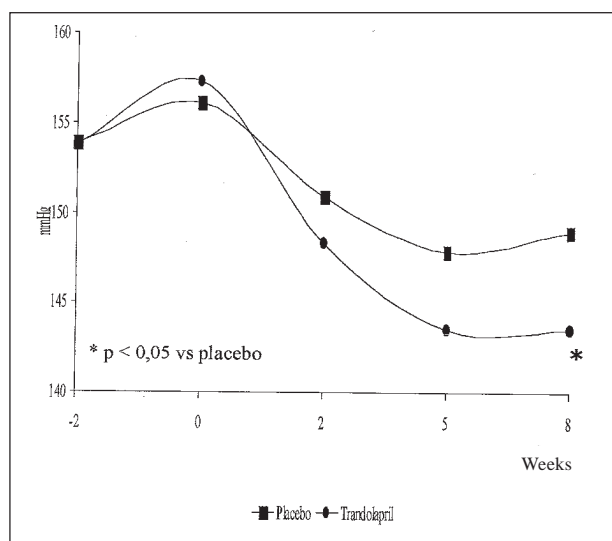


Figure 1 – Systolic blood pressure before and during placebo (n=135) or trandolapril (n=127) treatment.

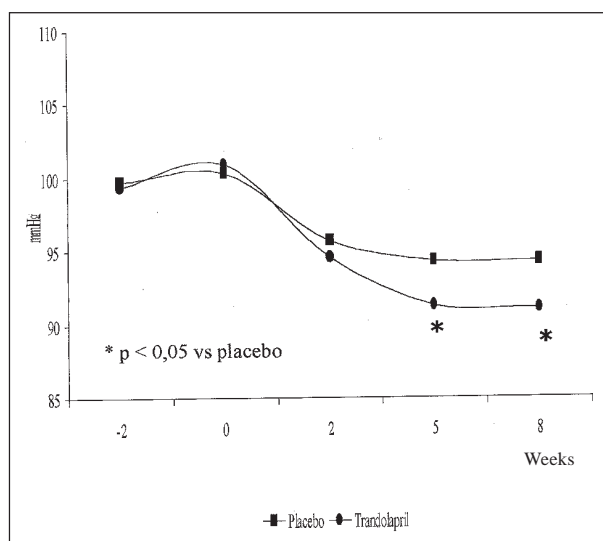


Fig. 2 – Diastolic blood pressure before and during placebo (n=135) or trandolapril (n=127) treatment.

teristics from different regions of the country, which might influence BP, mainly because of the decrease in the efficacy of ACE inhibitors in nonwhite subjects or in those with a high sodium intake.

However, our results showed that the efficacy of trandolapril was similar in white and nonwhite subjects. Thus, we observed that both BP reduction intensity and trandolapril-responsive patients (about 58%) observed in nonwhite patients (39% and 53% of patients in studies 1 and 2) were not different from white patients. Thus, in our study, BP response to conversion enzyme blockade with trandolapril was uniform, not being influenced by ethnic differences.

Although we did not measure salt consumption in our population, which should be very variable due to regional habits, we did observe differences in our study, when results among study centers from different regions of the country were compared.

Our results obtained through ABPM were in accordance with previous studies showing that the antihypertensive effect of trandolapril lasts 24h in those patients considered responsive to this ACE inhibitor.

In spite of the fact the duration of the antihypertensive effect of trandolapril, was evaluated in an open, non-placebo controlled manner which partially diminishes its statistical power, the results observed in study 2 are relevant because they complement the information gathered in study 1, corroborating previous observations of the literature<sup>5,6</sup> and results obtained concomitantly to study 1 in very similar populations.

In addition to being effective, trandolapril was shown to be a drug with good tolerability, because adverse events were not different from those observed with placebo use, even with the loss of follow-up of a very small number of patients. The side effect profile observed does not differ

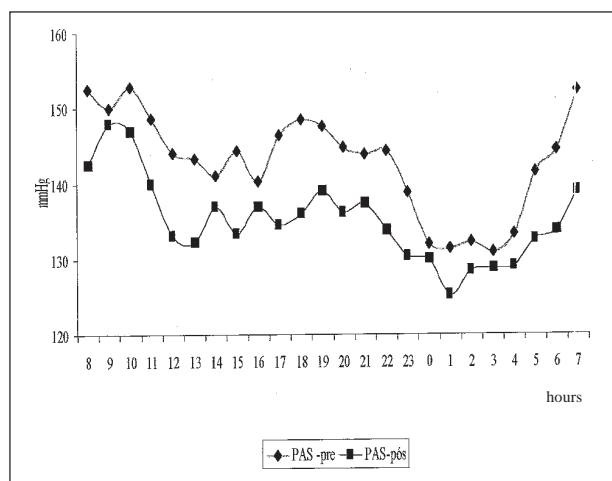


Fig. 3 – Hourly average of systolic blood pressure recorded during AMBP before and after 12-week treatment with trandolapril.

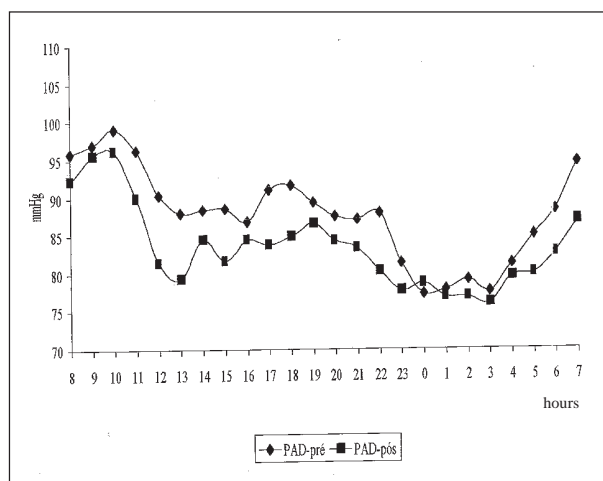


Fig. 4 – Hourly average of diastolic blood pressure during AMBP before and after 12-week treatment with trandolapril.

from those already described for trandolapril, as well as for other ACE inhibitors.

In conclusion our data show that, similar to data from other studies, trandolapril is an effective drug for blood pressure control, regardless of the characteristics of the study population, with a prolonged hypotensive effect and very good tolerability.

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