Morphine Sulphate Tablets for Chronic Pain Management: A Prospective Comparative study versus Anti-depressant

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Abstract: Objectives: To evaluate analgesic efficacy of oral morphine sulphate tablets (MST) alone versus combination with antidepressant (AD) for chronic pain management. Patients & Methods: The study included 360 patients had cancer pain and 167 were non-cancer patients. Initial pain score was evaluated using 10 points visual analogue pain scale (VAS). All patients received 4-week trial using AD, then patients showed significantly lower score (4-W score) with tolerable side effects continued on the used drug, otherwise shifted to MST alone or MST and AD combination and were re-evaluated. Patients developed MST-related side effects tried gradual dosage adjustment and re-evaluated. Patients on MST therapy were prescribed prophylactic laxative. Results: At 4-W evaluation, AD significantly reduced pain scores with tolerable side effects in 119 patients, 198 patients were shifted to MST alone and 210 patients received combined therapy. At 8-W evaluation, MST alone significantly reduced pain scores with tolerable side effects in 156 patients, while 42 patients developed side effects so MST dose was reduced by 50% and at 12-W pain scores were changed non-significantly but side effects became tolerable. Combined therapy significantly reduced pain scores with tolerable side effects of both drugs in 145 patients, 39 patients developed aggravation of AD-related side effects that was stopped and patients were maintained on MST alone and 26 patients complained of MS-related side effects, but responded to 50% reduction of MST dosage. At 12-W, 119 patients were maintained on AD only, 237 patients on MST alone and 171 patients were maintained on combination of both. Conclusion: MST as initial chronic pain therapy provided significant reduction of pain severity with dose-dependent side effects, while AD are not advocated as initial therapy for unpredictable therapeutic effect and high frequency of side effects and if mandatory it must be combined with MST.
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Introduction

Chronic pain, irrespective of its nature and cause, imposes challenge on pain therapists for varying mechanisms, modes of presentation, variable response to certain well-documented analgesics, [1, 2, 3]. Superimposed, various studies suggested that chronic pain patients always suffer affection disorders and other studies provided evidence that emotional regulation could help in alleviation of pain severity, [4, 5, 6] and this was the rational for the use of antidepressants as a line for chronic pain management.

The analgesic potency of opioids is well-documented and its use as a therapeutic modality for chronic pain syndromes despite being less than ideal because long-term use carries a risk of dependency and abuse, progressive increase of the dose of consumed drug and increases the risk for development of side effects; it is necessary and humanely especially in cancer pain patients and those with intractable non-cancer pain, [7, 8, 9].

On the other hand, antidepressants are not free off side effects that could hamper its long-term use and carries a similar risk for tolerability, [10] thus the rational for the use of combined therapy appeared to allow administration of the lowest effective dose with minimization of the frequency and severity of side effects.

The present prospective comparative study aimed to evaluate the analgesic efficacy of oral morphine sulphate tablets alone versus combined used of MST and antidepressant for management of patients with chronic pain.

Patients & Methods

After approval of the study protocol by the Local Ethical Committee, through the period from Jan 2008 till June 2009 patients attending Pain Clinic at Kasr Al-Eni Hospital for treatment of chronic pain, irrespective of its etiology and signed a written fully-informed consent about the study protocol were included. Patients who were on other lines of analgesia or received other opioids than MST or received MST in combination with other drugs were not enrolled in the study.

Patients were evaluated clinically concerning age, gender and type of pain whether cancer pain or non-cancer pain. Pain data including

character, radiation, onset, progress and types of previous management and its effects were collected.

Prior to study inclusion, pain severity was evaluated (Initial score), on the institutional 10 points visual analogue pain scale (VAS) with 0 equals no pain and 10 equals the worst intolerable pain. For patients who could not accommodate with VAS scoring graph, pain severity was evaluated with the verbal analogue scale with no pain equals zero, mild pain was arbitrarily evaluated as 25, moderate as 50 and severe as 75 and the worst intolerable pain as 100 on a 100-point graph.

According to the study protocol for pain management, all patients received a trial for 4-week duration using antidepressants and then treatment was modified according to the response in the form of evaluated VAS pain scores (4-W score) in comparison to the initial score and the frequency and severity or tolerability of associated side effects. Patients showed significantly lower 4-W score with tolerable side effects continued on the used drug, otherwise either shifted to MST alone or in combination with the used drug for synergism. Then patients were re-evaluated after another 4 weeks for their VAS pain scores (8-W score). Patients developed MST-related side effects but showed significant improvement on 8-W score tried gradual dosage adjustment till the appropriate dose the equalized efficacy versus side effects and re-evaluated 4-weeks thereafter (12-W score), time for pain severity and side effect stability. All patients assigned for MST therapy were prescribed prophylactic laxative prior to therapy initiation

Results

The study included 527 patients; 342 males (64.9%) and 185 females (35.1%) with a mean age of 46.5±6.7; 32-62 years. Three hundreds and sixty patients (68.3%) had cancer pain and 167 patients (31.7%) had non-cancer patients.

At 4-W evaluation, 119 patients (22.6%) showed significant improvement manifested as significant reduction of VAS pain scores with tolerable side effects; however, 408 patients (77.4%) were not satisfied and considered as failure for AD therapy alone. These 408 patients were divided into 2 groups; the first included 198 patients who were unsatisfied because both minimal reduction of VAS pain scores and prominent side effects were considered as complete failure of therapeutic target for a rate of 37.6% and were shifted to MST alone, while 210 patients had tolerable side effects but showed minimal reduction of VAS pain scores and were prescribed MST in addition to the previously used AD in the same dose.

At 8-W evaluation, 156 patients received MST alone showed significant reduction of VAS pain scores with tolerable side effects, while 42 patients despite the significant improvement of VAS pain scores were unsatisfied because side effects. For these 42 patients, the dose of MS was reduced by 50% and at 12-W evaluation VAS pain scores were non-significantly higher compared to 8-W scores, but still significantly lower compared to 4-W scores and side effects became tolerable without distress and were maintained on that adjusted dosage.

At 8-W evaluation 145 patients of those received combination of AD and MST showed favorable response in form of significant reduction of VAS pain scores with tolerable side effects of both drugs. On contrary, 39 patients developed aggravation of AD-related side effect despite the significant reduction of VAS pain scores and AD was stopped and at 12-W evaluation VAS pain scores were still significantly lower compared to 2-W scores despite being non-significantly higher compared to 8-W evaluation and these patients were maintained on MST alone. The remaining 26 patients complained of the MS-related side effects, but responded to MST dose reduction up to 50% reduction without significant effect on the VAS pain scores, (Table 1 & 2).

Table 1: Patients' distribution according to drugs used till achievement of maintenance drug type and dosage at 12-weeks after enrollment in the study

	Initial therapy	4-W evaluation		8-W evaluation			12-W evaluation
		Maintained	Shifted to	Maintained	Shifted to	MST Dose adjustment	
AD alone	527 (100%)	119 (22.6%)	0	119 (22.6%)	0	0	119 (22.6%)
AD & MST combination	0		210 (39.8%)	145 (27.5%)	0	26 (4.9%)	171 (32.4%)
MST alone	0		198 (37.6%)	156 (29.6%)	39 (7.4%)	42 (8%)	237 (45%)

Table 2: Mean (±SD) VAS pain scores reported since patients' enrollment till end of 6-weeks follow-up

Patients' groups	Initial	4-weeks			8-weeks			12-weeks		
	Mean±SD	Mean±SD	F	P	Mean±SD	F	P	Mean±SD	F	P
Total patients	47.1±13.3	37±16.3	1.534	=0.049	16±4.2	9.326	<0.001	18.8±4.1	0.823	>0.05
AD responders	44.5±11.3	14±3.6	2.507	=0.004	17.4±3.7	1.256	>0.05	18.1±3.8	1.375	>0.05
AD non-responders	47.9±13.7	43.7±11.8	1.469	>0.05						
MST & AD combination										
Good response & No SE (n=145)	49.2±14	42.4±11.2	1.335	>0.05	14.9±3.1*†	4.726	<0.001	19.8±4.3	1.295	>0.05
Good response & MST SE (Reduced MST dose; n=26)	50±12.7	47.3±12.2	1.114	>0.05	17.4±4.3	6.179	<0.001	19.8±4.1	1.324	>0.05
Good response & AD SE (Shift to MST alone)	50.2±13.8	46.2±11.4	1.479	>0.05	13.8±4	4.010	=0.002			
MST alone										
Good response & No SE (n=156)	46±13	43.1±12	1.274	>0.05	16.1±2.4	9.326	<0.001	17.3±3.8	1.334	>0.05
Good response but with MST SE (Reduced MST dose) (n=42)	46.6±15.8	46±12.7	0.926	>0.05	18.5±2.7	4.724	0.001	20.5±2.7	1.324	>0.05
Shifted from combination group								20.1±4.3	1.412	>0.05
Total	46.8±13.7	44.1±12.1	1.198	>0.05	17±3.9	10.64	<0.001	18.9±3.8	1.285	>0.05

Totally, at point of drug type and dosage stabilization at 12-W evaluation, 119 patients (22.6%) were maintained on AD only, 237 patients (45%) were maintained on MST alone and 171 patients (32.4%) were maintained on combination of AD and MST, (Figure 1). At 8-W evaluation, VAS pain scores were significantly ($p<0.05$) lower in patients received combined therapy compared VAS pain scores determined at 8-weeks in both AD alone and MST alone with significantly lower scores in MST group compared to AD group, (Figure 2).

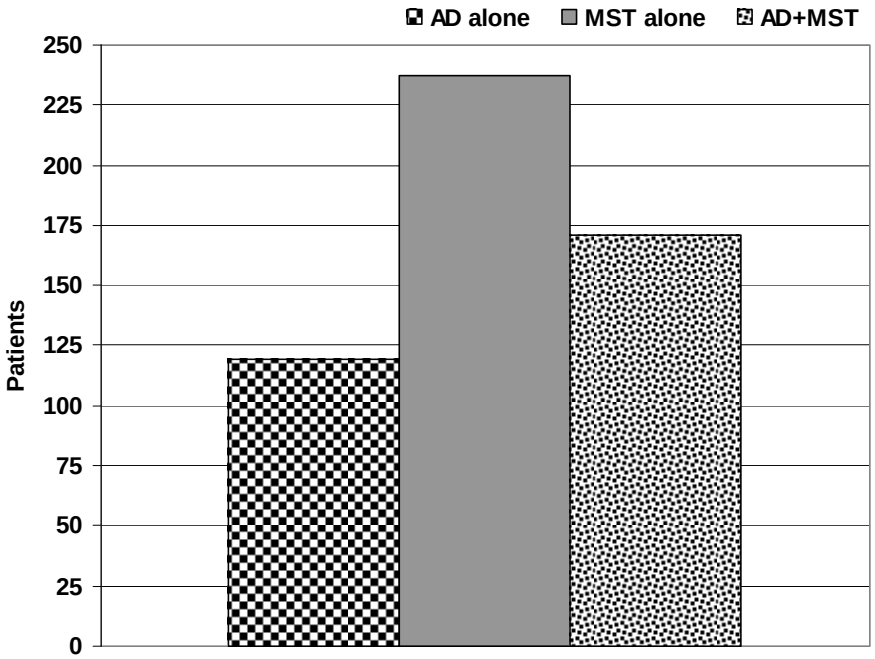

Figure 1. patients' distribution according to drug maintenance at 6-W evaluation

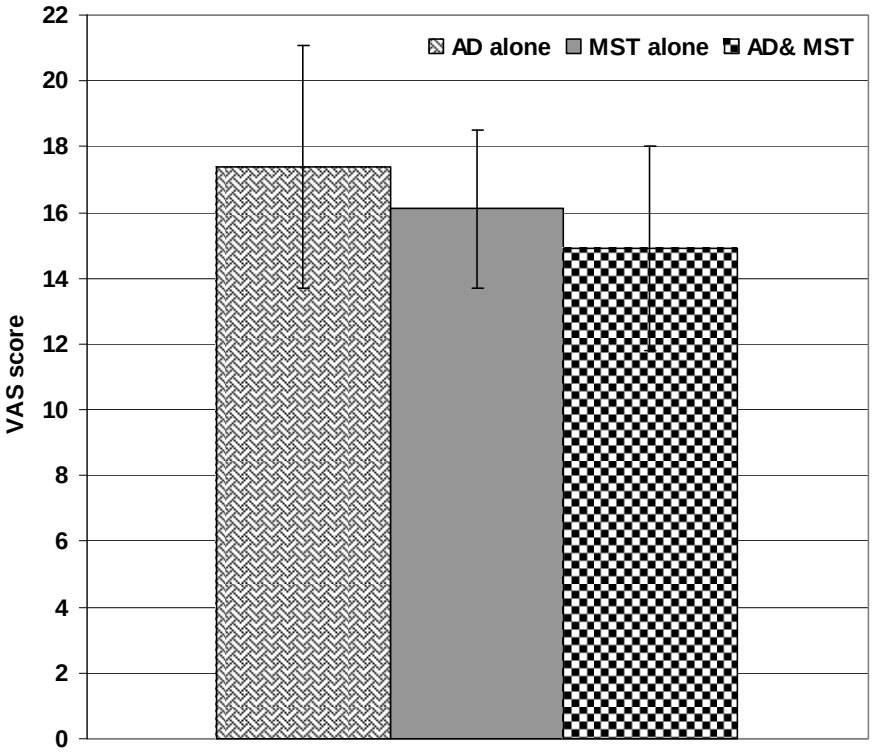

Figure 2. Mean (±SD) VAS pain scores of 8-w evaluation of the studied groups

Considering side effects as a limiting factor that may hamper continuation of therapy, side effects were reported in 198 patients started with AD and these patients refused to continue and prescribed MST despite the knowledge of its possible side effects. Another 39 patients were shifted from combination group to MST alone because of AD-related side effects for a total frequency of AD-related side effects of 237 of a total of 527 patients (45%). On contrary, out of 408 patients received MST side effects were reported by 68 of a total of 527 patients (16.7%) and these side effects were dose-related and became tolerable on 50% reduction of MST dose. Thus, MST pain therapy showed significantly (X^2=14.326 $p<0.001$) lower frequency of side effects compared to AD, irrespective of the mode of its use. Moreover, the frequency of side effects when MST used alone (21.2%) was significantly (X^2=3.71 $p<0.05$) lower compared to the frequency reported with AD when used alone (37.6%). However, there was non-significant (X^2=1.601, $p>0.05$) difference between the frequency of side effects of MST and AD, despite being in favor of MS, (Table 3).

Table 3: Patients' distribution according to the frequency of side effects of studied drugs either used alone or in combination

		Alone	In combination	Total
AD		198 (37.6)	39 (18.6%)	237 (45%)
MST		42 (21.2%)	26 (12.4%)	68 (16.7%)
Statistical analysis	X^2	3.71	1.601	14.326
	p	<0.05	>0.05	<0.001

Discussion

The present study was based on trial-&-error basis so as to achieve the most appropriate modality for management of chronic pain. The study encompassed 527 chronic pain patients all had a trial for 4 weeks using AD alone that succeeded to control pain with tolerable side effects in 119 patients and this effect was maintained till 12-week evaluation without significant change. Another 171 patients showed significant reduction of VAS pain scores at 8-weeks compared to that recorded at 4-weeks after 4 weeks of administration of combination of AD and MST. Thus AD provided clinical success rates of 22.6% and 32.4%, when used alone or in combination, respectively, with a total success rate of 55%.

These figures of chronic pain control using AD go in hand with various previous studies; *Oshima et al.,* [11] reported relief of persistent neuropathic tooth pain developed after undergoing endodontic procedure in 68.8% of studied patients and *Bajwa et al.,* [12] retrospectively reported favorable response in files of 76% of studied patients with neuropathic pain managed using AD. However, these both figures were superior to that reported in the current study and this could be attributed to patients' selection as both studies were selective for neuropathic patients; the actual target of AD therapy and *Bajwa et al.,* [12] intentionally excluded cancer pain patients while the current study was based on random methodology for patients' inclusion irrespective of type of pain and the main bulk of studied patients had cancer pain.

The reported significantly lower VAS pain scores when MST combined with AD than AD alone or MST alone indicated synergistic effect between both drugs, however, such synergism is from AD to the MST effect as evidenced by the more significant difference of the scores between AD&MST combination compared to AD alone versus MST alone and on reduction of MST dose VAS pain scores for patients received combination with reduced MST dose were better than those received reduced dose of MST alone. These findings were in line with that reported by *Hibi et al.,* [13] who found the classic antidepressant, amitriptyline, may help pain control by narcotics in elderly patients with chronic back pain from a vertebral osteoporosis fracture.

The reported synergism was proved experimentally by *Pettersen et al.,* [14] who reported that selective norepinephrine reuptake inhibitors can significantly increase the intensity and duration of morphine antinociceptive activity via both α_2-adrenergic and opioid receptors. Such synergism may be attributed to the effect of AD on affection with a favorable mood modulation and alleviation of apprehension with release of tension so that the effect of MST became more pronounced even with reduced dose. In support of such attribution, *Matsuzawa-Yanagida et al.,* [15] reported that chronic pain induced anxiety with changes in opioidergic function in the central nervous system and the selective serotonin reuptake inhibitor antidepressants are effective for treating anxiety associated with chronic neuropathic pain and these anxiolytic and antinociceptive effects were achieved by acting on different brain regions.

However, *Benbouzid et al.,* [16] experimentally provided another explanation for such

synergism that the antiallodynic effect of chronic antidepressant treatment is mediated by a recruitment of the endogenous opioid system acting through delta-opioid receptors; depending on these results there was a reciprocal synergism between both drugs that could explain the pronounced effect of combination over either drug alone.

Throughout the study, 68 patients received decreased MST dose by 50% to minimize side effects without significant change of the analgesic efficacy, this finding supported that previously reported by *Nissen et al.,* [17] who evaluated the use of and need for opioids in patients and reported a significant decrease in the mean total daily oral morphine equivalent prescribed on discharge 36.9 mg compared with that on admission 88.7 mg without significant effect on the analgesic efficacy

Unfortunately, the total frequency of AD-related side effects (45%) was significantly higher compared to total MST-related side effects (16.7%). Furthermore, the frequency of side effects was significantly higher with AD (37.6%) alone compared to MST alone (21.2%); a fact that the concomitant AD-related side effects overweighs the reduction of pain scores and point to the necessity of abounding AD use as first line of management. On contrary, combination of both MST and AD lessened the frequency of side effects of both, (12.4% and 18.6%, respectively) with concomitant improvement of pain control

These data go in hand with *Ikawa et al.,* [18] who found amitriptyline was effective in relieving pain associated with a somatoform pain disorder in the orofacial region, but the dose of amitriptyline may need to be as high as that used to treat a major depression with side effects frequency of 63.3%. In accordance with the current study, *Manchikanti et al.,* [19] reported a frequency of opioid-related side effects of 18% and 17% when used alone or in combination, respectively.

Considering opioid-induced bowel dysfunction is the most common complaint resulting from the actions of opioids within the gastrointestinal tract [20] and being unlike most other opioid adverse effects, tolerance does not develop with opioid-induced constipation, [21]; all patients assigned for MST administration were treated prophylactically to lessen the severity of constipation

The present study crossed some of limitations documented by other authors; being a prospective study crossed the limitation documented by *Bajwa et al.,* [12] whose study was a retrospective study design and the use of antidepressants as a part of multimodal treatment of pain and by *Manchikanti et al.,* [19] who evaluated a number of opioids with irregular pain distribution and considered the limitations of their study included the inability to incorporate multiple other drugs due to complicated nature with multiple groups and data collection and analysis and that the proportion of patients receiving methadone, oxycodone, morphine, and propoxyphene was low compared to hydrocodone. However, wide-scale study population was required for establishment of the obtained results.

It could be included that MST could be considered as appropriate initial chronic pain therapy providing significant reduction of pain severity with dose-dependent side effects that could be managed with minimal impact on its analgesic potency. On contrary, antidepressants are not advocated as initial therapy for unpredictable therapeutic effect and high frequency of side effects and if mandatory it must be combined with MST so as to achieve significant improvement of outcome with reduction of side effects.

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