Assessing the effectiveness of Yar ke extract in the detoxification of opiate addict by Traditional Medicine approach

O Myint Myint Than[1],Gaw Htet Doe[2],Win Myint[1], Tin Oo[2],

Wah Wah Win[2],

Kyaw Soe[1], Hla Myint[1],Theim Kyaw[1],Aung Myint[1] & Tin Nyunt[1]

1. Department of Traditional Medicine, 2. Department of Health

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INTRODUCTION

A.Tree

B. Stem

C.Extract

Drug consists of dried stem bark of *Sapium insigne* (Roxb.) Benth; Fam. EUPHORBIACEAE.

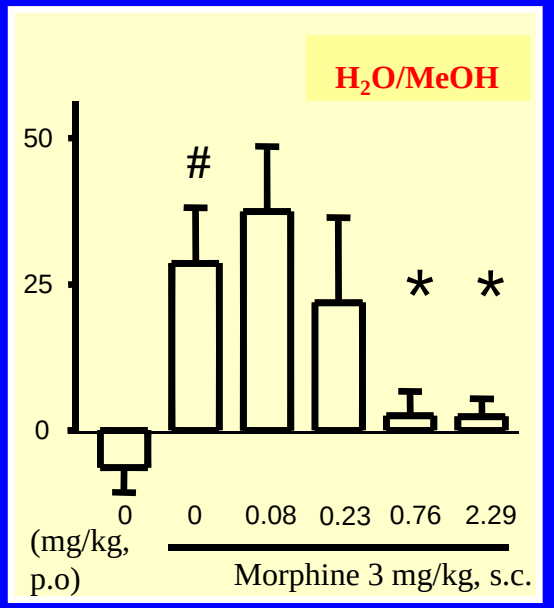
Other Names

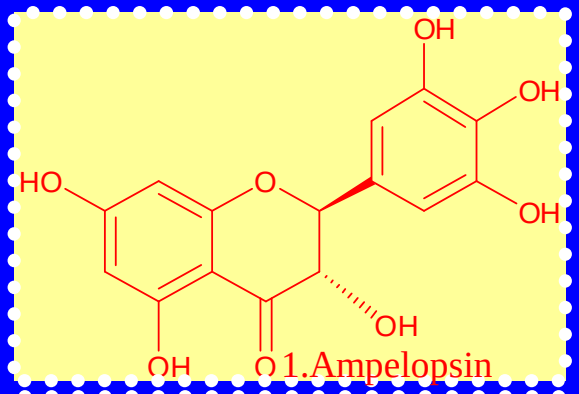
Myanmar Name : Thit Pyauk

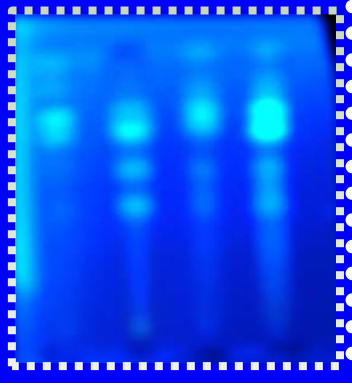
Shan Name : Yar Ke

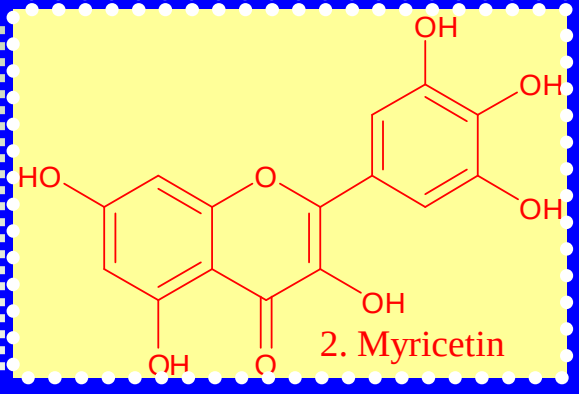
Pa O Name : Tasee Phray Tan

Scientific investigation on bark of Yar ke have been isolated five chemical constituents including two major flavonoids: myricetin and ampelopsin. Yar ke methanol soluble fraction of watery extract showed potent "anti-narcotic activities" based on its ability to counter the effect of morphine on nociception (pain perception) during tail-pinch test in mice (2003)









According a pilot study (1008-2009), three patients given Yar ke were found to be relieved from toxic action of opiate addiction within three to four days while the two patients under rational treatment were still suffering from withdrawal symptoms. Based on these information, clinical trial research project were implemented for safety and effective of Yar Ke in the detoxification of Opiate dependence (2009-2011) with permission of Institutional Ethical Committee meeting 1/2009 and supported by WHO.

OBJECTIVES

General objective

- To assess the efficacy for Yar Ke in opiate detoxification.
- To assess the safety of Yar Ke on organ systems.

Specific objectives

- To compare the opiate withdrawal symptom scores between opiate users who are detoxed using Yar Ke and those with Tincture of Opium
- To compare the effects between Yar Ke and Tincture of Opium on the liver and cardiovascular function during opiate detoxification.

Material & Methods

RESEARCH DESIGN & METHODOLOGY

1.**Study design**

- A Case-control observational clinical trial was conducted from (date) to (date) on 63 opiate dependent patients. Cases were assigned to each group according to the patients preferences.
- The control group -Standard treatment for opiate addiction with Tincture of Opium as the main opiate substitute
- The experimental groups -Yar Ke.

2. Study area

The Drug Treatment Unit of Sao San Tun General Hospital, Taunggyi, Shan State, Myanmar

3. Study period

Two years from September 2009 to August 2011.

4. Study population

Opiate users who fulfilled the diagnostic criteria for opiate addiction according to the Diagnostic and Statistical Manual IV (Revised edition, 2000) were designated as opiate addicts and were recruited into the study.

5. Sample size

Total : 63 patients

(43) cases received Yar Ke

(20) cases received Tincture of Opium

6. Inclusion criteria

- All opiate users who voluntarily request opiate detoxification by Yar Ke.
- All opiate users between 18 years and 50 years of age.
- All opiate users who give informed consent.
- All opiate users who are legally registered and ethically reviewed for management of opiate addiction.

7. Exclusion criteria

- All opiate users who are suffering from cardiac, hepatic and renal diseases.
- All opiate users who are severely malnourished.
- All opiate users who have co-morbid psychiatric disorders.
- All opiate users who have been receiving opiate detoxification by allopathic drugs.
- All opiate users who are also addicted to other drugs including alcohol.

8. Clinical end point

Absence of opiate withdrawal symptoms during a 48 hour period assessed by the Subjective Opiate Withdrawal Scale and Clinical Opiate Withdrawal Scale (COWS and SOWS, Handlesman et al.) and when two consecutive negative urine tests are obtained for opiates conducted 24 hours apart

9. Data entry & Data analysis

Data collected in paper format was manually entered into a database using Epi-Info Version 6.04d. Comparison of the two groups was done using Student's t-test for continuous variables and Chi-square test for categorical variables.

10. Instrument used for Opiate withdraw symptom measurement

1. The Subjective Opiate Withdrawal Scale
2. Clinal Opiate Withdraw Scale

11. Laboratory examinations

- Blood for complete picture
- Blood for ESR
- Liver function tests: Serum bilirubin, ALT and AST.
- Chest X-ray
- Blood pressure and ECG
- Ultrasound abdomen

12. Test drug

Semisolid prepared from the decoction of the bark of Yar ke. The decoction was prepared by boiling 8 kg of dried bark with 100 liters of water until 20 liters remain. Such semisolid 10 ml is equivalent to 4 gm of dried extract. The physico-chemical properties of the semisolid preparation were determined and recorded.

Result and Discussion

Socio-demographics of the study sample

Description	Yar Ke group	Control	P value	Remarks
Mean Age	32.04	34.1	0.64	ns
Marital status				
Never married	14	9		
Have married	29	11	0.33	ns
Education				
Mean years of education	2.72	6.30	0.002	ss

The mean age for Yar ke group and control group are 32 years and 34 years respectively.

Marital status – There are no sigficant difference between Test and control group with nearly half (47.6 %) are married and the rest are single.

The mean duration of education is 2.7 years for test and 6.3 years for control group. However, mean years of education has no effect on withdraw scores (SOWS and COWS).

Drug use characteristics of the study sample

The mean age of onset of drug used are 27.4 (test group) and 27.2 (control group) and the mean difference are not significant.

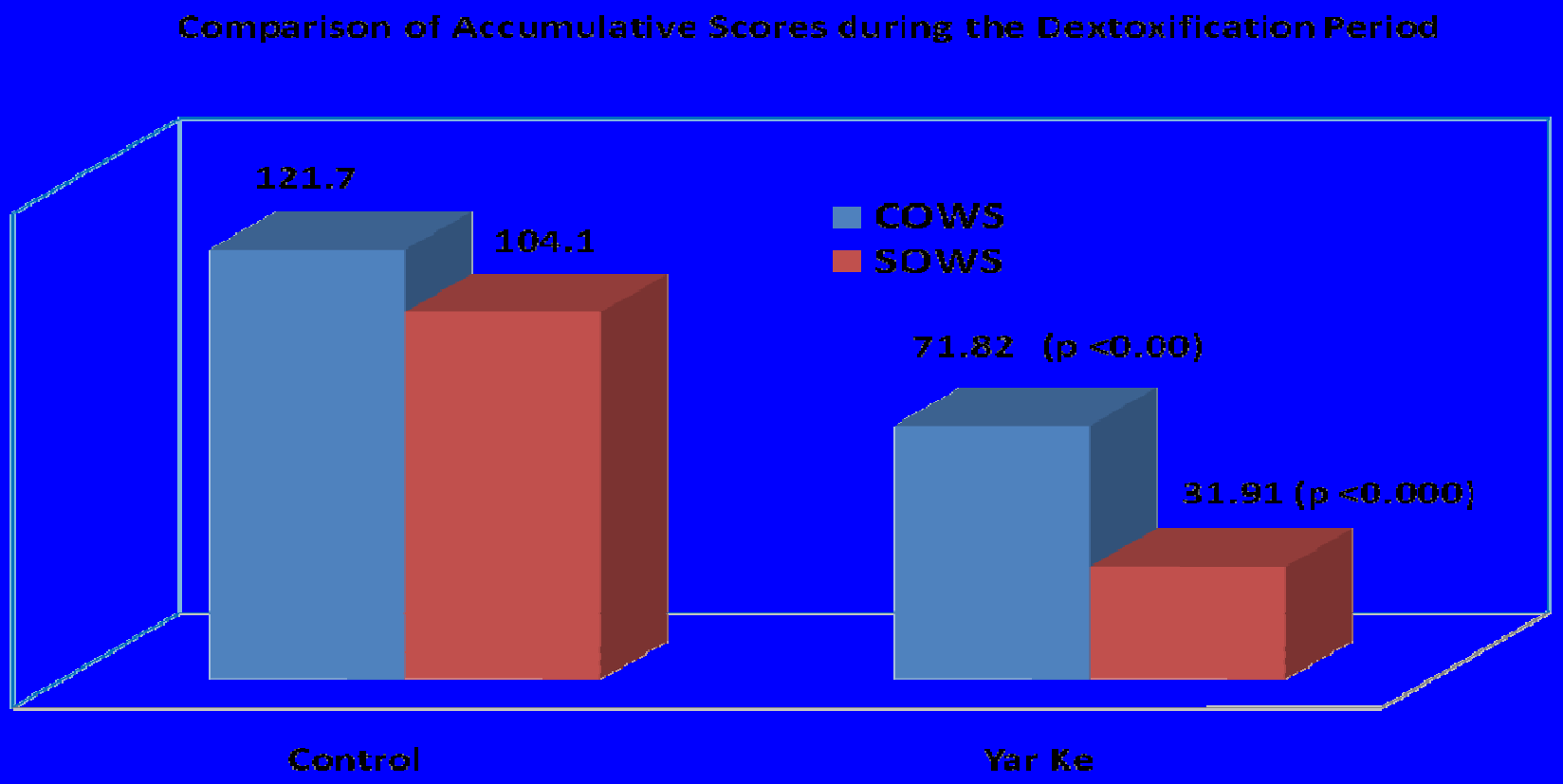
The mean duration of drug used is 4.9 yrs for test group and 6.9 yrs of control group. The mean differences of drug is not significant.

The mean daily dose of drug used is 4.2g for test group and 7.2 g for control group. The mean differences of daily opiate used is found to be sigficant. Testing for correction b/t mean daily opiate used with COWS and SOWS show R=0.46. This was not found to be at statistically significant level. However, stratified analysis on amount of daily opiate used was calculated.

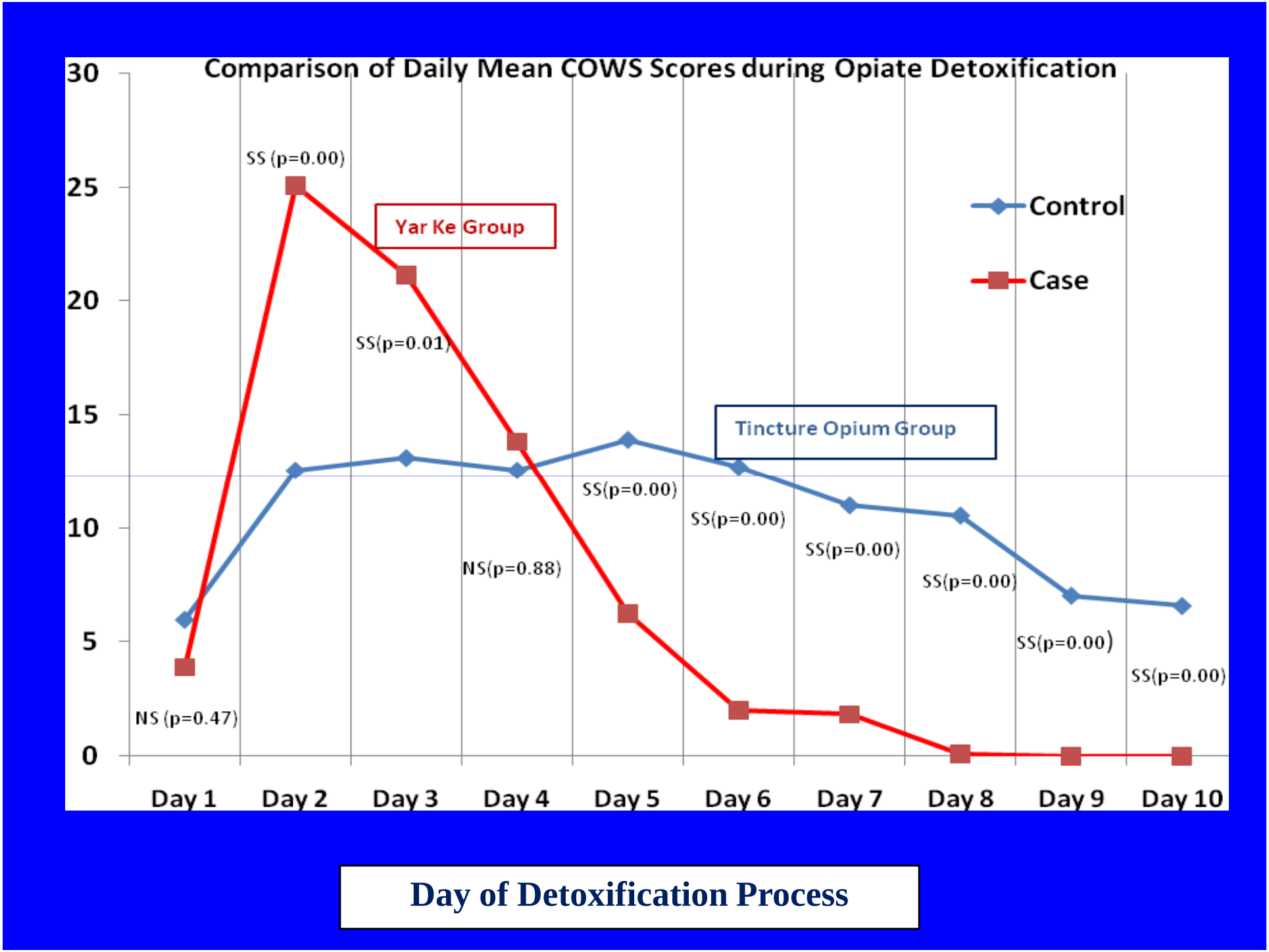
Motivation to stop drug use

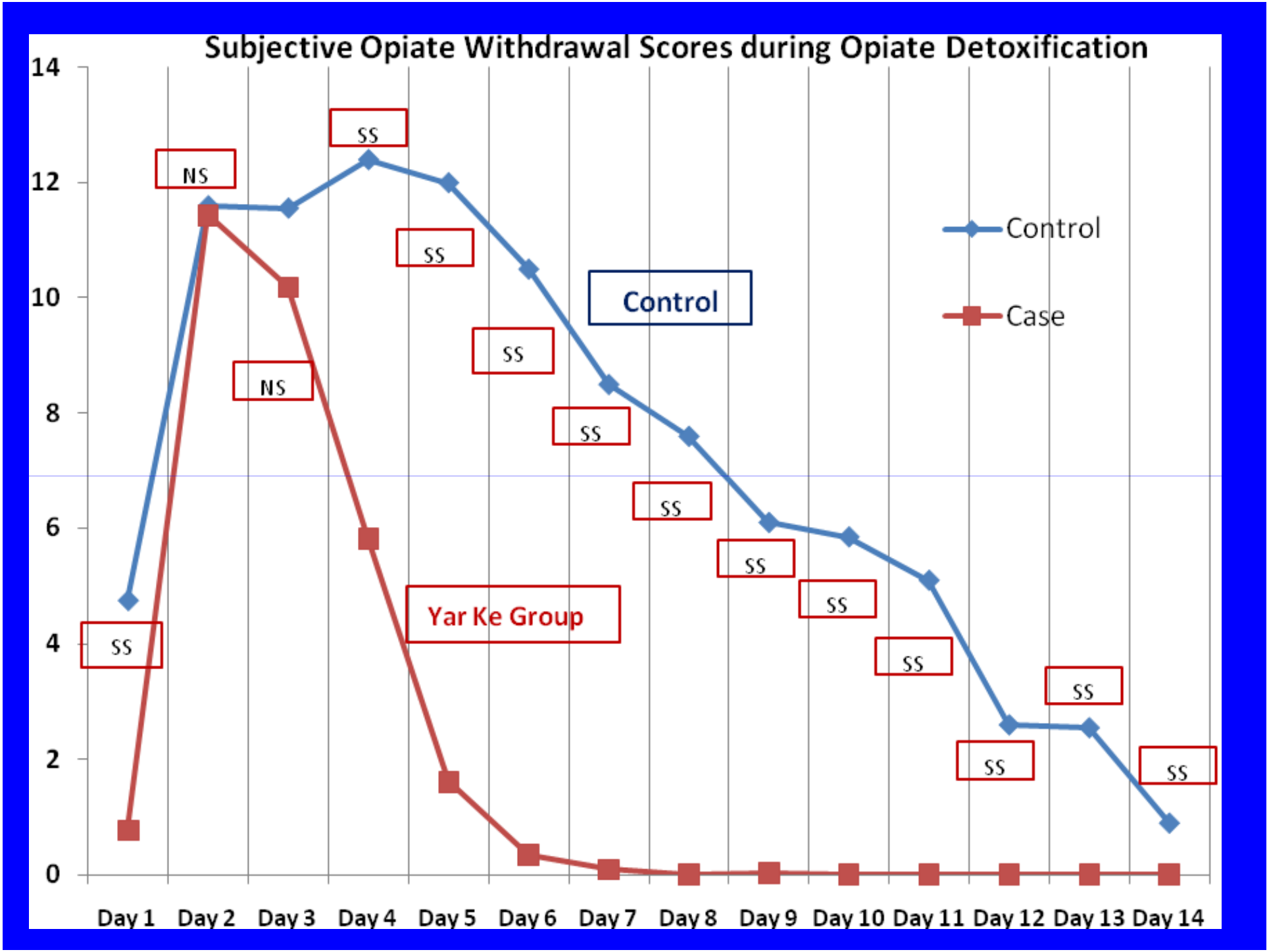
Mean scores on Change Motivation Readiness to seek treatment are comparable at 19.1 for test group and 18.5 for control group.

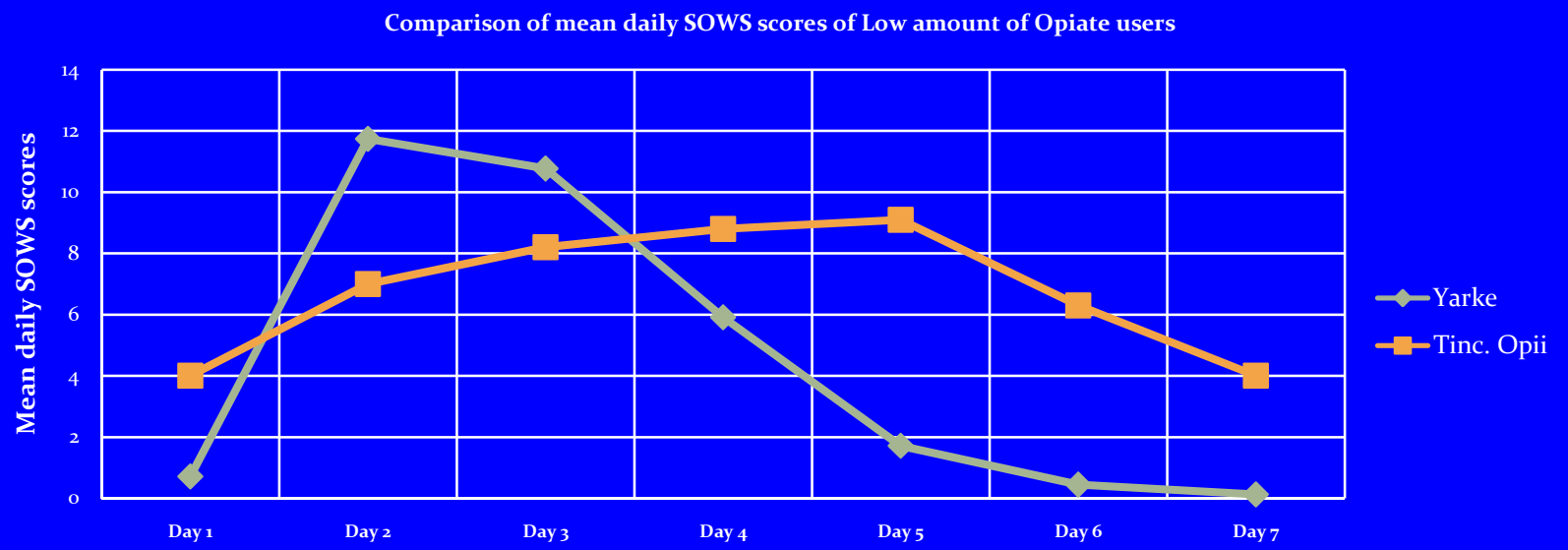
Comparison of Withdrawal Scores

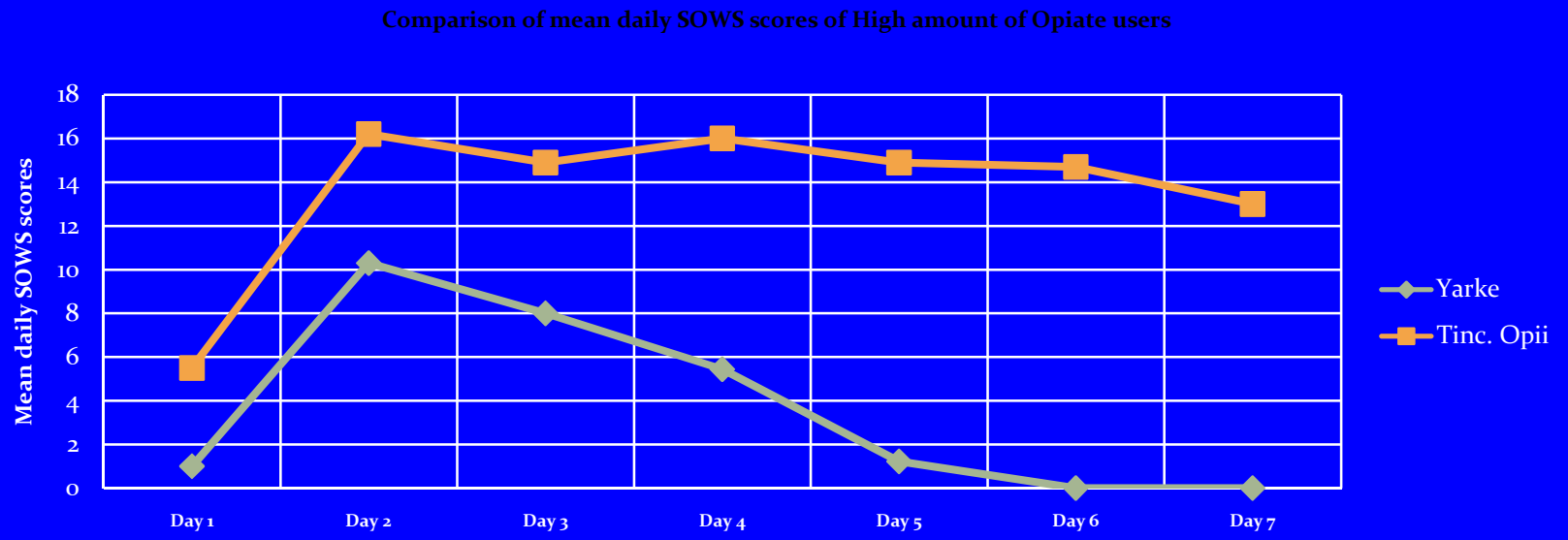


Over seven days detoxification for SOWS and COWS, test group shows lower score compared to control.


Comparison of Daily Mean COWS Scores during Opiate Detoxification
30
25
20
15
10
5
0
Control
Case
Yar Ke Group
Tincture Opium Group
SS (p=0.00)
SS(p=0.01)
NS(p=0.88)
SS(p=0.00)
SS(p=0.00)
SS(p=0.00)
SS(p=0.00)
SS(p=0.00)
SS(p=0.00)
NS (p=0.47)
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 10
Day of Detoxification Process

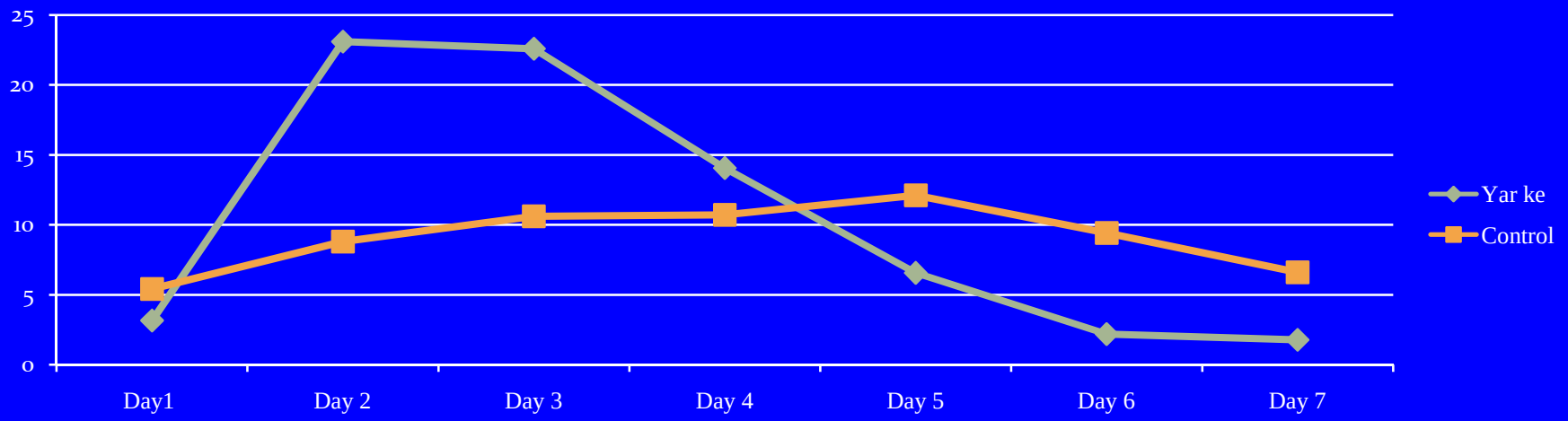

Subjective Opiate Withdrawal Scores during Opiate Detoxification
14
12
10
8
6
4
2
0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 10
Day 11
Day 12
Day 13
Day 14
Control
Case
Control
Yar Ke Group
NS
NS
SS
SS
SS
SS
SS
SS
SS
SS
SS
SS
SS
SS

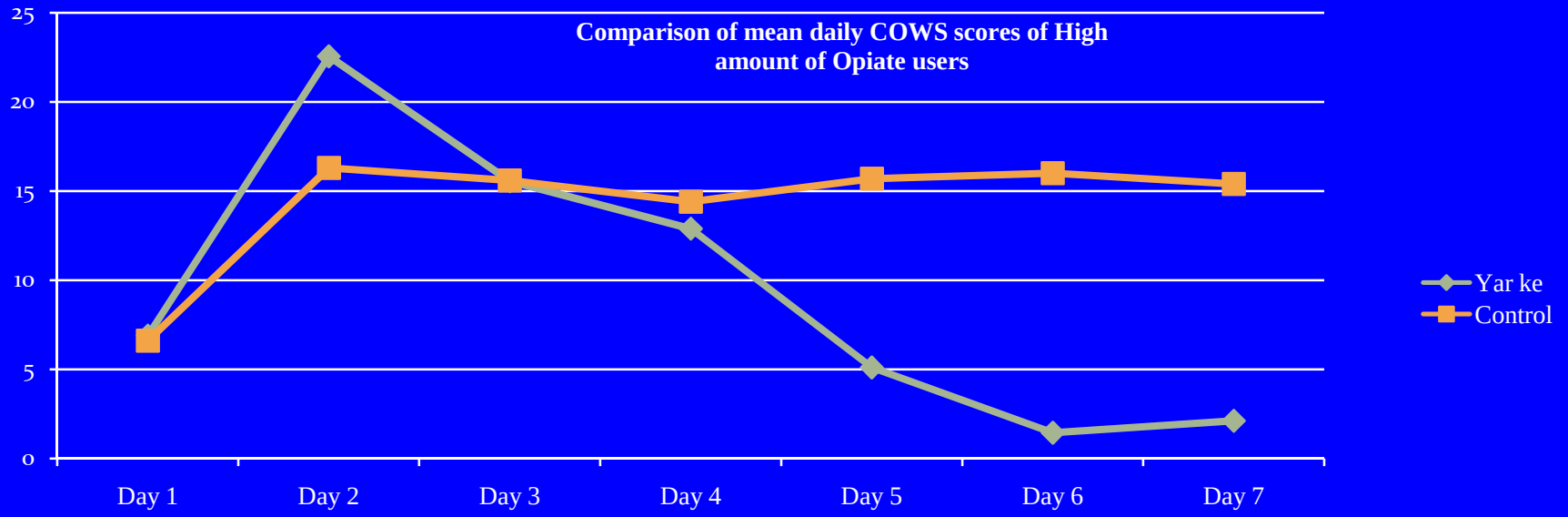




Correction between total SOWS scores and mean daily Opium used show that they are corrected at the rate of R= 0.48. This correction is not statistically significant. However, stratified analysis to adjust for mean daily opiate used has been calculated.

Comparison of mean daily COWS scores of Low amount of Opiate users





Correction between total COWS scores and mean daily Opium used show that they are corrected at the rate of R= 0.46. This correction is not statistically significant. However, stratified analysis to adjust for mean daily opiate used has been calculated.

Laboratory results

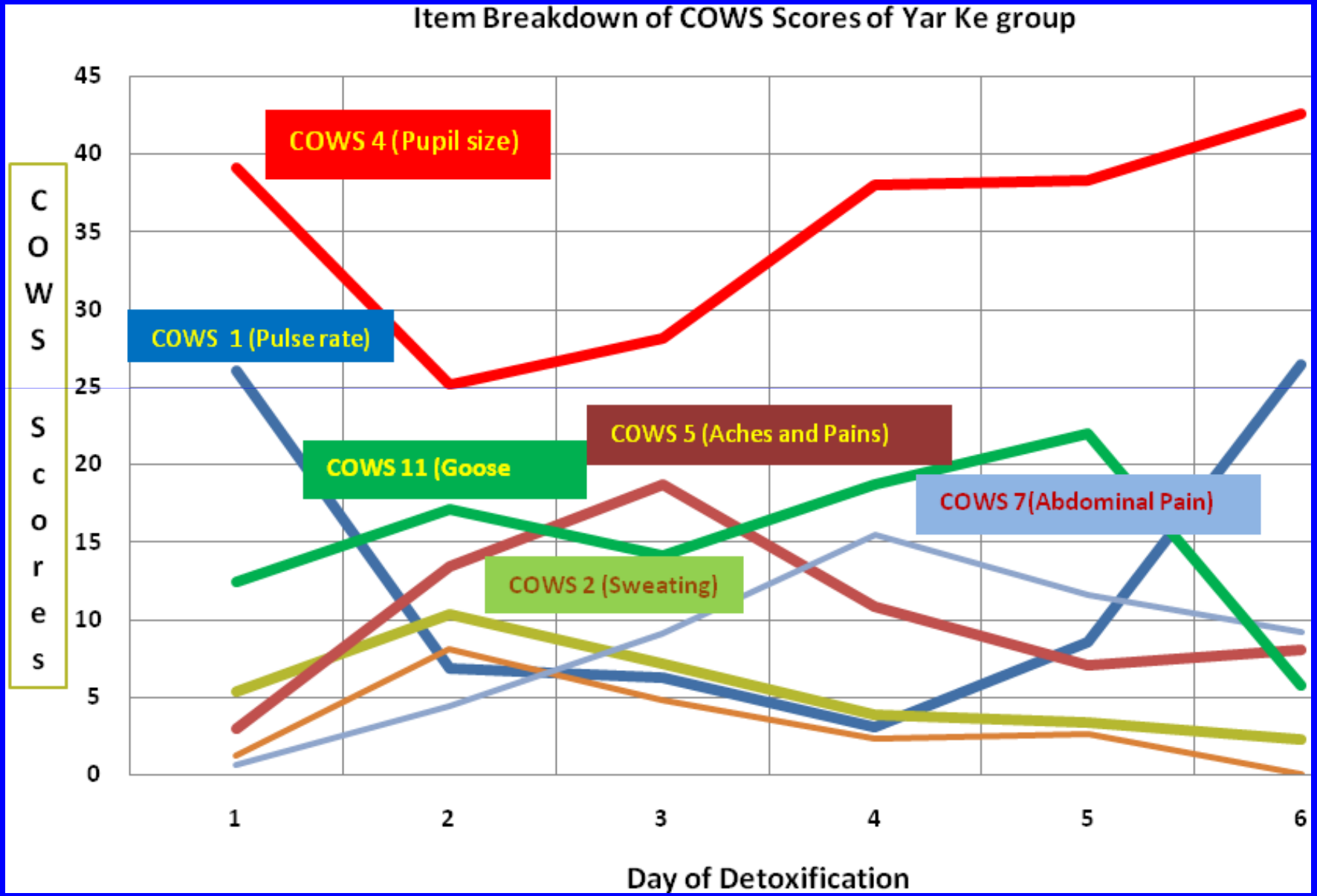
- **Blood tests**

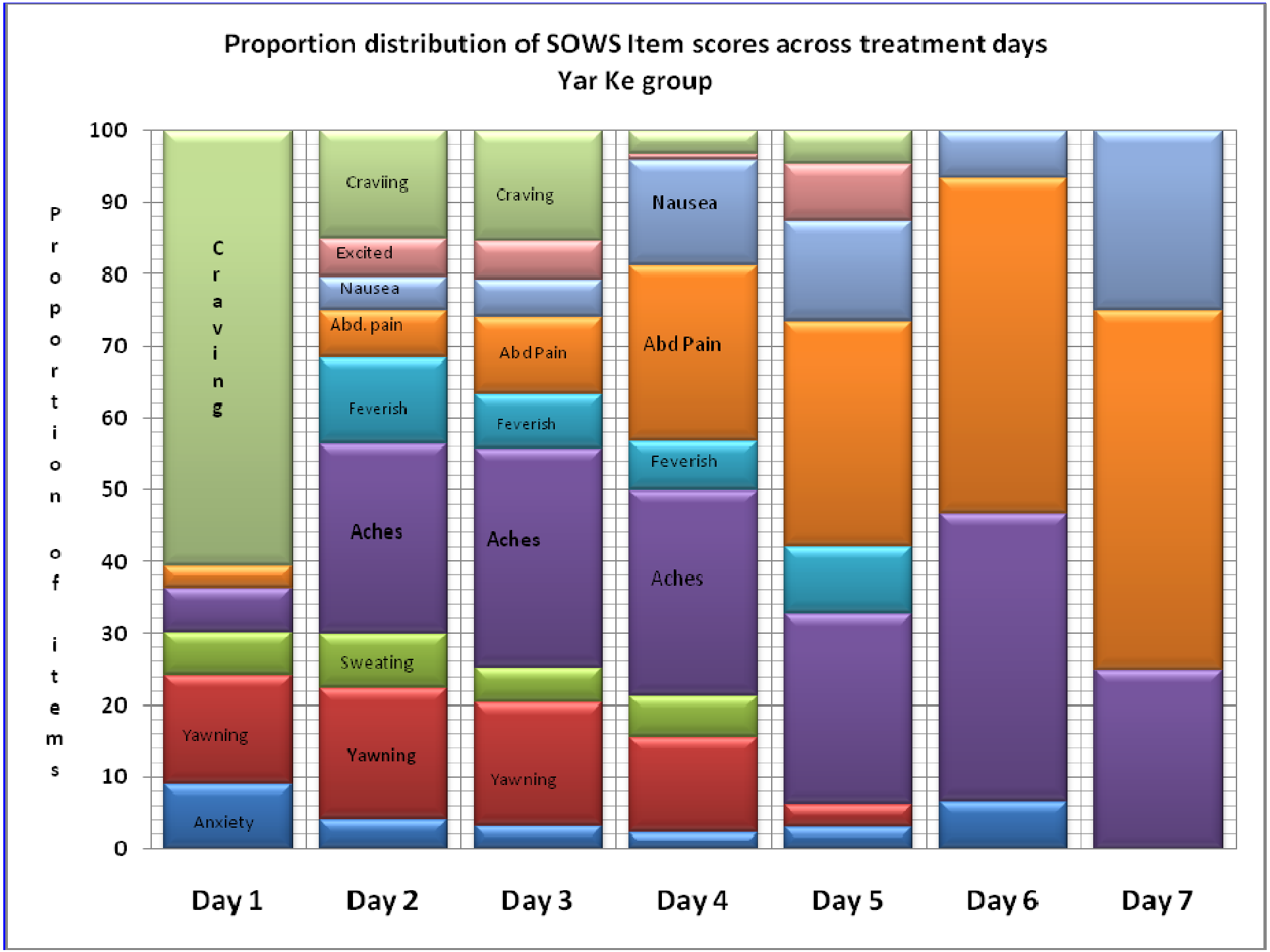
  There were no significant changes in the blood pictures of both groups

- **Liver Function tests**

❖The liver function tests results conducted before and after Detoxification for both Yar Ke and Control groups showed that, Yar Ke group had significantly reduced ALT levels and serum bilirubin levels than the Control group.

Item Analysis

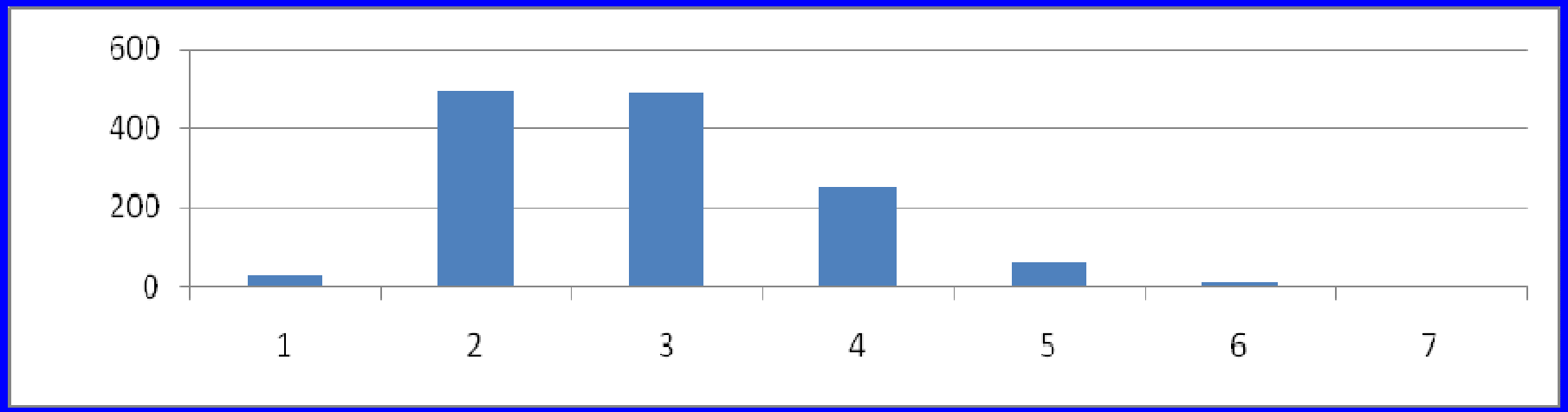



Proportion distribution of SOWS Item scores across treatment days
Yar Ke group
Proportion of items
100
90
80
70
60
50
40
30
20
10
0
Craving
Yawning
Anxiety
Craviing
Excited
Nausea
Abd. pain
Feverish
Aches
Sweating
Yawning
Craving
Abd Pain
Feverish
Aches
Yawning
Nausea
Abd Pain
Feverish
Aches
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7

On studying the items which contributed to these peak levels during Day 2, it was found that the Aches and Pains suffered by the study subjects contributed the highest proportion (26%), followed by Yawning (18%), Craving (15%), feeling Feverish (12%) and Sweating (8%).

During Day 3, the items which contributed to these peak levels did not change much when compared with the previous day; the Aches and Pains increased to 30%, while Yawning decreased slightly to 17%, Craving stayed the same at 15%, feeling feverish reduced to 8% and Sweating also reduced to 5%. The item which increased during Day 3 was the Abdominal Pain (11%). The excitement symptom also increased slightly to 6% from 5% the day before.

Item analysis of the SOWS scores



During the detoxification period, the mean SOWS scores of the Yar Ke group showed peak levels in Day 2 and Day 3 and then declining in Day4 to reach near zero levels in Day 6 and Day 7.

The mean SOWS scores reached during peak days of Day 2 was the only day that reached peak levels at the same level with that of the Control group

During the subsequent Day4 to Day 5,

- Aches and Pains
- Abdominal Pain
- Nausea

were the three symptoms which dominated the clinical presentation. By Day 6, the severity of the symptoms reduced to very low levels and the Nausea, Abdominal Pain and the Aches and Pains were the only symptoms that remained by Day 7.

DISCUSSION

Comparability of the two groups

Yar ke group

1. **Lower educated**
2. **Lower level of drug used**
3. **Lower scores-level of total suffering during the detoxification -4 days (“0” level in day-5)**
4. **Shorter period of time**

T O group

1. better educated
2. Higher level of drug used
3. Higher scores- level of total suffering during the detoxification -even at day -14
4. Longer period of time

Safety Profile of Yar Ke

❖ The results of serological tests conducted on various organ systems show that Yar ke does not have any deleterious effects on the haemopoietic systems and liver function. The detoxification process has been reported to have a certain level of stress on liver function as reported by TMPs.

❖The liver function tests results conducted before and after detoxification for both Yar Ke and Control groups showed that, Yar Ke group had significantly reduced ALT levels and serum bilirubin levels than the Control group.

❖This is suggesting that Yar Ke not only in safe to use in terms of liver effects, but may even have a therapeutic effect on liver function.

Development of opiate detoxification Regime

✓It is remarkable that opiate detoxification can be conducted by using Yar Ke alone, without any additional medication to relieve the withdrawal symptoms.

✓If a treatment regime using several traditional medicines which can allay the Pain and anxiety symptoms and be used along with Yar Ke, then, it has the potential of becoming the method of choice for opiate detoxification for opiate addicts living in the remote villages.

FUTURE WORKS

- Yar Ke is conducted to possess clinical effectiveness in the detoxification of opiate addicts. It should be further processed to develop a natural product for pharmaceutical application.

CONCLUSION

- Yar Ke has been found to be a promising extract from the bark which can be used in detoxification of opiate addicts.
- The strong points of Yar ke is the significatly shorter duration of the detoxification period needed, which translates into less cost, less cost in the need for additional medicines, shorter disruption from work which can also translate into shorter duration of no income for a daily wager, and also easy accessibility to detoxification from his or her opiate addiction for people living in remote villages which are situated very far from the drug treatment centres.

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