DISCUSSION
CHAPTER -IV
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The primary objectives of this study were to investigate the effects of Very early mobilisation (commenced within 48 hours of stroke) coupled with the routine care on the Prevention of adverse effects, Activity of daily living, and the Level of disability following acute stroke. The secondary objectives of this study were to investigate the effects of Very early mobilisation coupled with the routine care on the Quality of Life (OoL), Depression and anxiety following acute stroke.

The results of this randomized controlled trial demonstrated that early and frequent out of bed activities coupled with the routine care prevented adverse effects associated with the immobility, augmented return of the activities of daily living and reduced disability further improved quality of life and reduced depression and anxiety (p<0.05) than the routine care alone following acute stroke. Therefore we rejected null hypothesis and accepted experimental hypothesis.

At three months follow-up, the maximum scores in terms of effect sizes occurred for the Barthel index of activity of daily living, Modified rankin scale (mRS), Medical outcomes short form 36 v2 (PCS Score); however little score or non-significant in terms of effect size was noted for the Medical outcomes short form 36 (MCS Score), and the Hospital anxiety and depression rating scale (Anxiety and Depression sub scale) at 3 month of follow-up after the stroke.
The findings of the present study contradict with the studies conducted by Bernhardt J et al. [53] Langhorne P et al. [57] where they found that very early mobilisation had a non-significant effect size (SES) on the independence in activities of daily living at three months following the acute phase of stroke.

The participants aged between 30 years to 90 years, with the mean age of 61.30 years (SD= 11.15) were included in the study, 99 subjects (49 male, 50 female) in the Intervention group and 98 (49 male, 49 female) in the Routine care group were remained at the three months follow-up and their data was analyzed. The mean age of the intervention group subjects was 60.20 years (SD= 10.94) and that of the Routine care group subjects was 62.42 years (SD= 11.30). Age, sex, and affected side of the stroke were homogenous among the groups.

Approximately 45% of the individuals with the stroke were admitted within 24 hours of stroke symptom onset and initiated first mobilisation < 24 hours. Further, 55% of the individuals with the stroke were admitted within 48 hours of stroke symptom onset and initiated first mobilisation < 48 hours.

The time of initiation of the mobilisation of the present study go along with the study conducted by the AVERT trial by Bernhard et al [53] (<24 hours), SEVEL trial by Herisson et al [65] (<24 hours), AKEMIS trial by Sundseth et al [98] (<24 hours), Lausanne trial by Diserens et al [60] (<24 hours), and VERITAS trial by Langhorne et al [57] (<24 hours), and Poletto et al [61] (<48 hours).
In the current study 90% of the individuals with the stroke belong to the either mild or moderate severity (<16) measured at admission with National Institute of Health Stroke Scale (NIHSS).

The severity of the stroke of the present study go along with the study conducted by the AVERT trial by Bernhard et al. [53] (80% of subjects were <16 on NIHSS), SEVEL trial by Herisson et al.[65] (Average of 7.2 of NIHSS, at admission for the intervention group), AKEMIS trial by Sundseth et al.[98] (82% of subjects were < 16 on NIHSS at admission), Lausanne trial by Diserens et al. [60] (14.4 of NIHSS at admission), and Poletto et al. [61] (80% of subjects were < 18 on NIHSS at admission).

The mean duration of the hospital stay of the subjects who underwent very early mobilisation coupled with routine care was 8.65 days and that of the routine care was 11.27 days. Mean difference of the duration of the hospital stay noted was 2.61 days between the groups (p<0.05). Thus length of the hospital stay for the intervention group was less compared to the routine care group (Table 7). 

The length of the hospital stay stroke participants of the present study go along with the study conducted by the AVERT trial by Bernhard et al. [53] (very early mobilisation group median (IQR) =16 (5-44) days and standard care group median (IQR) =18 (6-43) days), VERITAS trial by Langhorne et al. (Early mobilisation group median (IQR)=10 (5-14) and Control group median (range) =12 (6-16)), Lausanne trial by Diserens et al. [60] (Early protocol mean (SD)=13.7 (6.82) and Delayed protocol, 11.71 (4.66) with no significance) and Poletto et al. [61] (Intervention group median and IQR = 8 (5-14) and control group= 10 (4-25),
However in our study we achieved statistical significance between groups.

The terminology ‘Very Early Mobilisation’ or ‘Early Rehabilitation’ following cerebrovascular accident is ambiguous. Many countries stroke guidelines stated, starting as early as possible rehabilitation may have potential benefits on recovery process and minimize secondary complications. The term ‘early’ is very vague, it starts from >24 hours to three months of stroke onset and the term ‘repetitive’ is also not clear, many guidelines says individuals with stroke are advised to be active and out of bed as many times as possible and tolerated by the stroke survivor. The term ‘very early mobilisation’ and ‘early mobilisation’ are interchangeable. The term mobilisation is not clear to health care professionals, traditionally mobilisation thought to be passive and active movements of the limbs/joints. \[48, 50\]

However some researchers pointed out that any activity which is performed in the bed including passive and active movements are not ‘mobilisation’ and they defined ‘mobilisation’ as out of bed activities including upright sitting, standing and walking. \[49, 50\]

In this study the term “very early” is defined as initiation of mobilisation within the first 48 hours of stroke symptom onset. The term “mobilisation” is stated as upright activities such as sit upright, stand upright, sit to stand transfer and walking activities perform throughout the day. The term ‘Very Early Mobilisation’ (VEM) is defined as out of bed upright activities including sit upright, sit to stand, stand upright, and walking within 48 hours of post-stroke.
In this study 208 individuals with acute stroke were randomized into the Intervention group (103) and the routine care group (105). At the three months follow-up, total 5.28% (11) participants were lost to follow-up, among that 1.92% (4) of the intervention group and the 3.35% (7) of the routine care group. Therefore current study has maximal compliance (94.7%) of subjects at three months follow-up and very few subjects drop outs (5.28%).

Minimal clinical importance difference (MCID) of Modified Barthel Index (0-20) used in stroke subjects was 1.85. These values, if apply to the original Barthel Index (0-100), approximately 9.25. However in this study we achieved 41.75% improvement on BI score (0-100) at the time of discharge and 48.39% at three months follow-up after stroke.

Minimal clinical importance difference (MCID) values are not established for the Modified rankin scale (mRS), Medical outcome short form 36, and Hospital anxiety and depression rating scale in stroke subjects. However in this study, we achieved 12.92% improvement on mRS score (0-6) at the time of discharge and 13.29% at three months follow-up, 5.16% improvement on PCS of SF-36 score at the time of discharge and 10.25% at three months follow-up, 16.9% improvement on MCS of SF-36 score at the time of discharge and 14.2% at three months follow-up. 21.56% improvement on HADS-Anxiety score at the time of discharge and 9.89% at three months follow-up. 18.29% improvement on HADS-Depression score at the time of discharge and 21.55% at three months follow-up after acute stroke. Thus current study results point out that intervention group had minimal clinical importance difference in outcome measures used in the study.
Comparison with related research

The current study has some similarities with the Bernhard J et al AVERT trail, \cite{53} we adopted early mobilisation protocol including early and repetitive practice of vertical activities such as sitting out of the bed, sit upright, stand upright and walking. Further monitoring of the safety vital measures at the beginning, during and at the end of mobilisation initial three days of the stroke onset.

However current study is different from AVERT trial, such as, current study was single center, parallel group randomised control trial, with the aim of mobilising stroke subjects within 48 hours of stroke onset. We used original barthel index scale for measuring freedom in ADL, quality of life was measured with SF -36 v2, depression and anxiety was measured with HADS tool, and disability was measured with Modified rankin scale (0-6).

However in the AVERT trial by Bernhard et al \cite{53}, modified rankin scale was used as a primary outcome measure for measuring death and level of disability, modified barthel index (0-20) was used to measure functional capacity, Tyedin et al \cite{62} was used HRQoL for measuring health related quality of life, Cumming TB et al \cite{63} was used Irritability depression and anxiety rating scale to measure the mood in stroke subjects.

Bernhard J et al. \cite{97} conducted a very large scale multicentre randomized control trial on effect of early and frequent mobilisation on reduction of death rate and disability following acute cerebrovascular accident. Their study revealed
surprise results that outcomes at three months, very early high intensity repetitive mobilisation along with usual care started within twenty four hours after stroke reported more fatalities than usual care.

In the current study delivery of upright activities which are initiated within 48 hours of stroke onset was tolerated by the most of the subjects and practical to implement early after the stroke.

The findings of the present study go along with the study conducted by Bernhardt J et al. [53] and Langhorne P et al. [57] Poletto SR et al. [61] found that very early and frequent mobilisation started within twenty-four hours of cerebrovascular accident symptom onset is practical and not harmful.

Prevention of Adverse Events and Very early mobilisation

In this study participant with stroke reported adverse events such as, Shoulder pain (22.3%), Urinary tract infection (14.2%), Constipation (13.7%), Fall (12.2%), Contractures (10.2%), Pressure sores (8.6%), and Pneumonia (7.1%). Both the groups reported very few serous, life threatening events such as another stroke, intra cerebral bleeding, and seizures (<9%) during first three months of cerebrovascular accident. Furthermore the intervention group reported total 144 adverse events, whereas the routine care group total 144 adverse events were reported at three months follow-up. Thus, it is evident that the intervention group subjects experienced less number of adverse events than the routine care group. However results found that no statistical significance difference between groups, p-value for above given complications was >0.05.
The findings of the present study go along with the study, D Sorbello et al.\textsuperscript{[92]} did a randomized controlled trial to explore whether very early mobilisation affected immobility related complication type, amount and severity in the first twelve weeks after the cerebrovascular accident. And the results showed as falls were routinely seen the problem, and the number of bedridden complications was associated with length of hospital stay. These results are consistent with our study findings, however in our study painful shoulder, urinary tract infection, falls, and constipation was commonly reported adverse events in the first three months following acute stroke.

The findings of the present study go along with the study, Poletto SR et al.\textsuperscript{[61]} did a pilot RCT on harmless and practicality of early mobilization following acute ischemic stroke. Their study results showed that frequency of immobility related complications and death were alike in the early mobilisation group and the routine care group.

A possible explanation for reduction in immobility related adverse events in the intervention group, could be attributed to the more chance to practice sitting out of bed, transfer to the toilet, standing and walking, which may have contributed to preventing/less chance to develop bed rest related adverse events after stroke.\textsuperscript{[120-123]}

**Freedom in activities of daily living and Very early mobilisation**

In the current study, the median difference (Discharge- admission) of Barthel index score for intervention group was 30 and median difference (three month follow-up-admission) was 45 and for the routine care group median
difference scores were 20, and 32.50 respectively. Between group comparisons of barthel index scores, shown the statistical significant difference at p<0.05.

65% of the subjects in the intervention group reported freedom in the activity of daily living (BI score >80) at discharge, and 87.9% of subjects at three months follow-up. Further Barthel index score had moderate effect size at discharge (0.50) and large effect size (0.87) at three months follow-up among groups.

Similar findings were reported by Chippala and Sharma [58], Cumming et al. [56]

The findings of the present study go along with the study, Chippala and Sharma [58] (2016) conducted a prospective randomized control trial in India on 83 subjects with acute cerebrovascular accident, compared early and repetitive mobilisation which was initiated within 24 hours of stroke onset with the routine care, concluded that 85% of early mobilisation group subjects were improved independence in activities of daily living (p<0.05).

The findings of the present study go along with the study conducted by Cumming TB et al. [56] in a randomized controlled trial found that very early mobilisation group had better effect on independence in activities of daily living (Barthel Index) at 3 months compared with the standard care subjects (p=0.008). However, at the end of one year Barthel Index Scores were not statistically significant.
The findings of the present study contradict with the various studies conducted by Bernhardt J et al. [53] Langhorne P et al. [57] Herisson F et al. [65], Sundseth et al. [98], Morreale et al. [141] where they found that very early mobilisation had no significance difference (p<0.05) on the independence in activities of daily living at three months following the acute phase of stroke.

The possible mechanism for improvement in freedom of doing activities of daily living with the very early mobilisation could be; firstly, an early and frequent task oriented activity may help to be physically active within and out of bed initial days of the stroke, Secondly early activity may stimulate the formation of new neural pathways, allowing earlier brain recovery and neural plasticity. [121]

Disability and Very early mobilisation

Current RCT results demonstrated that the intervention group is helpful in improvement of the level of disability at discharge and at three months follow-up after the cerebrovascular accident than the routine care group (p<0.05).

Our study results found that early and frequent mobilisation coupled with the routine care group, 79.8% of the participants of the intervention group reported good outcome (mRS score 0-2) at discharge compared to the 32.7% of subjects in the routine care group. Furthermore 92.9% of subjects in the intervention group reported good outcome (mRS score 0-2), at three months follow-up, compared to the 74.5% of subjects in the routine care group. Thus results clearly point out that intervention group participants were achieved better
good outcome on level of disability at discharge and at three month follow-up than the routine care group.

The present study results contradicts the findings of the Barnhart J et al. AVERT trial, Poletto et al, Morreale et al Herisson et al. SEVEL trial, Sundseth et al AKEMIS trial.

The results of the present study contradict with the study Morreale et al. performed a RCT in Italy on 340 subjects with acute stroke, with the objective of comparing early rehabilitation which was initiates inside 24 hours of stroke onset with routine care (received routine care for first four days, than initiated early rehabilitation after four days of the stroke onset). Concluded that level of disability measured on mRS at 3 months found to be no significance difference between groups (p>0.05).

The findings of the present study contradict with the study conducted by Bernhardt J et al. where they found that very early upright activity group reported poor outcome in disability and death at three months following the acute phase of stroke.

The findings of the present study contradict with the most recent single-center, randomized control trial performed by Herisson F et al. (2016) aimed to compare the effect of early out of bed sitting activity initiated within a day with progressively sitting activity started third day of ischemic stroke onset. Their study results suggest that early upright activity is useful in ischemic stroke survivors. However no distinction found among interventions in support of a favorable
outcome on modified rankin scale (0-2) score, barthel index and adverse events reported at three months post ischemic stroke. Further they also stated that early sitting procedure was safe and feasible.

The findings of the present study go against with the study, Poletto SR et al. [61] did a pilot RCT on harmless and practicality of early mobilization following acute ischemic stroke. Their study results showed that death and disability measured on modified rankin scale (mRS) were alike in the early mobilisation group and the routine care group (p>0.05).

Quality of Life and Very early mobilisation

We found that VEM coupled with the routine care had a better quality of life (Physical and Mental Composite Scores of SF-36) than the usual care (p<0.05). Further we also found that moderate effect size at discharge and large effect size at 3 months follow-up for PCS score of SF-36 among groups. Greater size achieved at discharge for MCS score of SF-36. However no effect on MCS SF-36 at three months follow-up among groups.

The present study findings were supported by the findings of the Tyedin K et al. [62] who performed a stage II randomized control trial on 71 subjects with cerebrovascular accident, with an objective to explore the consequence of VEM on the HRQoL. They concluded that VEM group improved long term quality of life especially independent physical functioning after stroke.

Similar findings were found in 2016 Hokstad A et al. [99] did a prospective cohort multi-centre study on 390 subjects with cerebrovascular accident in 143
Norway, to find out the association between the higher the amount of early and frequent out of bed activities and good outcome (mRS), Participation limitation (HRQoL) at 3 months following stroke? Their trial results authenticated that there was strong association of early and higher the amount of upright activity and good outcome (mRS), QoL after stroke.

The potential explanation for improvement in quality of life with the very early mobilisation could be; improving independence in ADL. An early and frequent functional activity may help to stimulate the formation of new neural pathways, allowing earlier brain recovery and neural plasticity. The potential explanation for improvement in quality of life with the very early mobilisation could be; improving independence in ADL. An early and frequent functional activity may help to stimulate the formation of new neural pathways, allowing earlier brain recovery and neural plasticity. Earlier studies have established that induction of proteins is associated with greater neuroplasticity within the first two weeks after the onset of stroke.

Depression, anxiety and Very early mobilisation

We found that VEM coupled with the routine care reduced depression and anxiety at discharge (seven days) and at follow-up (three months) than the routine care alone (p<0.05). Moreover, these findings were also strongly correlate with previous study results of Cumming TB et al. who studied the effect of VEM on anxiety, depression and irritability following acute stroke reported that at seven days depression was reduced significantly with the intervention group, however at three months and at one year follow-up non-significant difference was obtained for depression, anxiety and irritability.

Several plausible explanations for this effect are VEM may augment independence in ADL and quality of life, decreased frequency of immobility related complications and disability. As a result, stroke survivors may experience
less depression and anxiety. Very early and increased mobilisation directly reduces the risk of depression and finally, it can be attributed to the extra care and companionship further motivation they received in the additional VEM group.

Harms/Side effects reported in this study:

During the hospital stay no subjects were reported fatality, and serious life threatening events. However few subjects reported postural hypotension during early upright activities, for such cases mobilisation was immediately discontinued and positioned them to be supine in the bed. Further, adverse events reported in the intervention group subjects were advanced age category, severe stroke and associated with multiple co-morbidities. Thus delivering of early mobilisation is safe and practical in acute cerebrovascular subjects.

Strengths of the study:

Prospective randomized controlled trial with the concealed allocation. There was blinding of all assessors who measured at least one key outcome. The groups were similar at baseline for the most demographic and clinical characteristics of acute stroke survivors. Dropout rate at the three months follow-up was less than 6%.

Limitations of the study:

There are several limitations related to this study. Subjects recruited were not the representatives of the whole stroke population (Individuals with severe aphasia, who deteriorated within the first hour of admission to the hospital were not included in this study), longer (> 3 months) follow-up were not undertaken, Recording of the dosage of mobilisation was not done due to inadequate resources. We could not monitor the activity during discharge from the hospital to three months follow-up period. No blinded subject and physical therapist.