



Department of Anesthesia
Intensive care and pain management

Comparative study between Gabapentin, Midazolam and Granisterone in management of post operative nausea and vomiting in C.S

Thesis

Submitted for partial fulfilment of MD Degree
in Anaesthesia

Submitted by

Eman Atia Eltoukhy

M.B.B.Ch – M.Sc in Anaesthesia - Ain Shams University

Under Supervision of

Prof. Dr. Nahed Effat Youssef Salama

*Professor of Anaesthesia , Intensive Care and Pain Management
Faculty of Medicine - Ain Shams University*

Prof. Dr. Ahmed Mohamed Elsayed Elhennawy

*Professor of Anaesthesia , Intensive Care and Pain Management
Faculty of Medicine - Ain Shams University*

Dr. Hanan Mahmoud Farag Awad

*Assist. Professor of Anaesthesia , Intensive Care and Pain Management
Faculty of Medicine - Ain Shams University*

Dr. Heba Fouad Abd Elaziz Toulan

*Lecturer of Anaesthesia , Intensive Care and Pain Management
Faculty of Medicine - Ain Shams University*

**Faculty of Medicine
Ain Shams University**

2020



Acknowledgments

*First and foremost, I feel always indebted to **Allah**, the **Most Beneficent** and **Merciful** who gave me the strength to accomplish this work,*

*My deepest gratitude to my supervisor, **Prof. Dr. Nahed Effat Youssef Salama**, Professor of Anaesthesia, Intensive Care and Pain Management, Faculty of Medicine - Ain Shams University, for her valuable guidance and expert supervision, in addition to her great deal of support and encouragement. I really have the honor to complete this work under her supervision.*

*I would like to express my great and deep appreciation and thanks to **Prof. Dr. Ahmed Mohamed Elsayed Elhennawy**, Professor of Anaesthesia, Intensive Care and Pain Management, Faculty of Medicine - Ain Shams University, for his meticulous supervision, and his patience in reviewing and correcting this work,*

*I must express my deepest thanks to **Dr. Hanan Mahmoud Farag Awad**, Assist. Professor of Anaesthesia, Intensive Care and Pain Management, Faculty of Medicine - Ain Shams University, for guiding me throughout this work and for granting me much of her time. I greatly appreciate her efforts.*

*I can't forget to thank with all appreciation **Dr. Heba Fouad Abd Elaziz Toulan**, Lecturer of Anaesthesia, Intensive Care and Pain Management, Faculty of Medicine - Ain Shams University, whom tirelessly and freely gave comments on various drafts of this piece of work,*

*Special thanks to my **Family** members for their continuous encouragement, enduring me and standing by me.*

List of Contents

<i>Subject</i>	<i>Page No.</i>
List of Abbreviations.....	i
List of Tables.....	iii
List of Figures	viii
Introduction	1
Aim of the Work.....	5
Review of Literature	
GIT changes during pregnancy	6
Pathophysiology of post-operative nausea and vomiting (PONV).....	17
Prevention of PONV	32
Pharmacology of drugs used.....	51
Subjects and Methods	72
Results.....	79
Discussion	112
Conclusion.....	133
Summary	134
References	139
Arabic Summary	—

List of Abbreviations

<i>Abbr.</i>	<i>Full-term</i>
APAIS	: Amsterdam Preoperative Anxiety and Information Scale
ASA	: American society of anaesthesiologists
CS	: Caesrean section
BZD	: Benzodiazepine
Ca⁺²	: Calcium
CINV	: Chemotherapy-induced nausea and vomiting
CNS	: Central nervous system
CSF	: Cerebrospinal fluid
CTZ	: Chemoreceptor trigger zone
CYP450	: Cytochrome P450
ECG	: Electrocardiogram
FDA	: Food and Drug Administration
GABA	: Gamma-aminobutyric acid
GERD	: Gastro-esophageal reflux
GI	: Gastrointestinal
GIRK	: G-protein-coupled inwardly rectifying potassium
H	: Histamine
IASP	: International Association for the Study of pain
ICU	: Intensive care units
IV	: Intravenous
M	: Muscarine
N₂O	: Nitrous oxide
Na	: sodium

NACS	: Neonatal Neurologic and Adaptive Capacity Score
NICU	: Neonatal intensive care unit
NK-1	: Neurokinin
NMDA	: N-methyl-D-aspartate
NRS	: Numerical rating scale
NSAIDs	: Non-steroidal anti-inflammatory drugs
NSCSA	: National Sentinal Caesarean Section Audit
P-6	: pericardium-6
PACU	: Post anaesthesia care unit
PDNV	: Post-discharge nausea and vomiting
PON	: Postoperative nausea
PONV	: Postoperative nausea and vomiting
POV	: Postoperative vomiting
SNRIs	: serotonin and nor-adrenaline reuptake inhibitors
SSRIs	: selective serotonin reuptake inhibitors
$t_{1/2}$: Terminal half life
TDS	: Transdermal scopolamine
TIVA	: Total intravenous anaesthesia
5-HT	: 5-hydroxytryptamine
5-HT₃	: 5-HT subtype 3 receptor

List of Tables

Table No.	Title	Page No.
Table (1):	Risk score for PONV in adults	27
Table (2):	Simplified risk score for PDNV in adults.....	29
Table (3):	Simplified risk score for POV in Children. Simplified risk score.....	31
Table (4):	Apgar scoring system.....	75
Table (5):	Modified Ramsey sedation score.....	76
Table (6):	Demographic data of studied patients.....	80
Table (7):	Relation between Belveille as (No symptoms – Nausea –Retching - Vomiting) with Treatment groups after 2 hrs.....	81
Table (8):	Relation between Belveille as (No symptoms – Nausea –Retching - Vomiting) with Treatment groups after 4 hrs.....	82
Table (9):	Relation between Belveille as (No symptoms – Nausea –Retching -Vomiting) with Treatment groups after 6 hrs.....	83
Table (10):	Relation between Belveille as (No symptoms – Nausea –Retching -Vomiting) with Treatment groups after 8 hrs.....	84
Table (11):	Relation between Belveille with rescue antiemetic as (no drugs given – Granisetron 4mg, ranitidine 50mg) with Treatment groups after 2 hrs.	85

Table (12):	Relation between Belveille with rescue antiemetic as (no drugs given – Granisetron 4mg, ranitidine 50mg) with Treatment groups after 4 hrs.	86
Table (13):	Relation between Belveille with rescue antiemetic as (no drugs given – Granisetron 4mg, ranitidine 50mg) with Treatment groups after 6 hrs.....	87
Table (14):	Relation between Belveille with rescue antiemetic as (no drugs given – Granisetron 4mg, ranitidine 50mg) with Treatment groups after 8 hrs.....	88
Table (15):	Relation between Pain Score Scale with Treatment groups after 2 hrs.....	89
Table (16):	Relation between Pain Score Scale with Treatment groups after 4 hrs.....	90
Table (17):	Relation between Pain Score Scale with Treatment groups after 6 hrs.	91
Table (18):	Relation between Pain Score Scale with Treatment groups after 8 hrs.....	92
Table (19):	Relation between Pain Score Scale with Granisetron and Gabapentin as a confirmatory test after 4 hrs.....	93
Table (20):	Relation between Pain Score Scale with Granisetron and Gabapentin as a confirmatory test after 6 hrs.....	94
Table (21):	Relation between Pain Score Scale with Granisetron and Gabapentin as a confirmatory test after 8 hrs.	94

Table (22):	Relation between Pain Score Scale with Granisetron and Midazolam as a confirmatory test after 4 hrs.....	95
Table (23):	Relation between Pain Score Scale with Granisetron and Midazolam as a confirmatory test after 6 hrs.....	95
Table (24):	Relation between Pain Score Scale with Granisetron and Midazolam as a confirmatory test after 8 hrs.....	96
Table (25):	Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with treatment groups after 2 hrs.	97
Table (26):	Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with treatment groups after 4 hrs.	98
Table (27):	Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with treatment group after 6 hrs.....	99
Table (28):	Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with treatment group after 8 hrs.....	100
Table (29):	Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with Granisetron and Gabapentin as a confirmatory test after 4,6 and 8 hrs.	101

Table (30):	Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with Granisetron and Midazolam as a confirmatory test after 4,6 and 8 hrs.	102
Table (31):	Number of doses of rescue analgesic in 8 hrs.....	103
Table (32):	Relation between Ramsey as (anxious agitated – awake cooperative–semi asleep-asleep with response - asleep with sluggish response - no response) with Treatment groups after 2 hrs.....	104
Table (33):	Relation between Ramsey as (anxious agitated – awake cooperative–semi asleep-asleep with response - asleep with sluggish response - no response) with Treatment groups after 4 hrs.....	105
Table (34):	Relation between Ramsey as (anxious agitated – awake cooperative–semi asleep-asleep with response - asleep with sluggish response - no response) with Treatment groups after 6 hrs.....	106
Table (35):	Relation between Ramsey as (anxious agitated – awake cooperative–semi asleep-asleep with response - asleep with sluggish response - no response) with Treatment groups after 8 hrs.....	107
Table (36):	Relation between Apgar Score as (Score = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) with Treatment groups after 1 min.....	108

Table (37):	Relation between Apgar Score as (Score = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) with Treatment groups after 5 min.	109
Table (38):	Relation between postoperative amnesia as (no amnesia - amnesia) with Treatment groups.	110
Table (39):	Relation between postoperative amnesia as (no amnesia - amnesia) with Controland Gabapentin as a confirmatory test.	111
Table (40):	Relation between postoperative amnesia as (no amnesia - amnesia) with Controland Midazolam as a confirmatory test.	111

List of Figures

<i>Figure No.</i>	<i>Title</i>	<i>Page No.</i>
Figure (1):	Pathophysiology of PONV	17
Figure (2):	Simplified risk score for PDNV in adults.....	29
Figure (3):	Simplified risk score for POV in Children. ...	31
Figure (4):	Algorithm for management of postoperative nausea and vomiting	36
Figure (5):	P6 acupressure point location	47
Figure (6):	Chemical structure of Gabapentin	51
Figure (7):	Chemical structure of Midazolam and Diazepam	57
Figure (8):	Chemical structure of granisetron hydrochloride	66
Figure (9):	Numerical rating scale.	77
Figure (10):	Relation between age and weight (mean)	80
Figure (11):	Relation between Belville as (No symptoms – Nausea –Retching -Vomiting) with Treatment groups after 2 hrs.	81
Figure (12):	Relation between Belville as (No symptoms – Nausea –Retching - Vomiting) with Treatment groups after 4 hrs.....	82
Figure (13):	Relation between Belville as (No symptoms – Nausea –Retching - Vomiting) with Treatment groups after 6 hrs.....	83

Figure (14): Relation between Belville as (No symptoms – Nausea –Retching -Vomiting) with Treatment groups after 8 hrs.	84
Figure (15): Relation between Belville with rescue antiemetic as (no drugs given – Granisetron 4mg, ranitidine 50mg) with Treatment groups after 2 hrs.	85
Figure (16): Relation between Belville with rescue antiemetic as (no drugs given – Granisetron 4mg, ranitidine 50mg) with Treatment groups after 4 hrs.	86
Figure (17): Relation between Belville with rescue antiemetic as (no drugs given – Granisetron 4mg, ranitidine 50mg) with Treatment groups after 6 hrs.	87
Figure (18): Relation between Belville with rescue antiemetic as (no drugs given – Granisetron 4mg, ranitidine 50mg) with Treatment groups after 8 hrs.	88
Figure (19): Relation between Pain Score Scale with Treatment groups after 2 hrs.	89
Figure (20): Relation between Pain Score Scale with Treatment groups after 4 hrs.	90
Figure (21): Relation between Pain Score Scale with Treatment groups after 6 hrs.	91
Figure (22): Relation between Pain Score Scale with Treatment groups after 8 hrs.	92
Figure (23): Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with treatment groups after 2 hrs. ...	97

Figure (24): Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with treatment groups after 4 hrs.....	98
Figure (25): Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with treatment groups after 6 hrs.....	99
Figure (26): Relation between Pain Score with rescue analgesic as (no drugs given – meperidine 1mg/kg IM) with treatment groups after 8 hrs.....	100
Figure (27): Types of pain score with action with times to use drugs.	103
Figure (28): Relation between Ramsey as (anxious agitated – awake cooperative–semi asleep–asleep with response - asleep with sluggish response - no response) with Treatment groups after 2 hrs.	104
Figure (29): Relation between Ramsey as (anxious agitated – awake cooperative–semi asleep–asleep with response - asleep with sluggish response - no response) with Treatment groups after 4 hrs.	105
Figure (30): Relation between Ramsey as (anxious agitated – awake cooperative–semi asleep–asleep with response - asleep with sluggish response - no response) with Treatment groups after 6 hrs.	106

Figure (31): Relation between Ramsey as (anxious agitated – awake cooperative–semi asleep–asleep with response - asleep with sluggish response - no response) with Treatment groups after 8 hrs.	107
Figure (32): Relation between Apgar Score as (Score = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) with Treatment groups after 1 min.	108
Figure (33): Relation between Apgar Score as (Score = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) with Treatment groups after 5 min.	109
Figure (34): Relation between postoperative amnesia as (no amnesia - amnesia) with Treatment groups.	110

Abstract

Background: Caesarean section is one of the most prevalent surgical procedures among women. Pain, nausea and vomiting are the most common adverse effects of surgery. In the recent past, Gabapentin has been used to reduce pre-operative anxiety, acute postoperative pain, postoperative opioid requirements, postoperative nausea and vomiting (PONV) and delirium. Numerous studies have reported that Midazolam effectively prevents PONV. The use of midazolam not only may reduce the incidence of PONV but may also provide an anxiolytic and amnestic effect.

Aim of the Work: to compare between Gabapentin, Midazolam and Granisetron safety and efficacy in managing PONV.

Patients and Methods: This study started with 90 Pregnant females ASA II selected to compare between Gabapentin, Midazolam and Granisetron safety and efficacy in managing PONV for a parturient undergoing a caesarean section under spinal anesthesia, during the period of the study from 1st January 2018 to 31st December 2018 at Faculty of Medicine, Ain Shams University Hospitals, Gynecology and Obstetrics Hospital. patients were randomly divided into 3 equal groups; Gc: control group received Granisetron 40 ug/kg intravenous immediately before induction of anaesthesia and Group Gm: Midazolam group received Midazolam 20ug/kg intravenous immediately before induction of anaesthesia and Group Gg: Gabapentin group received a capsule of 600 mg orally one hour before induction of anaesthesia and a syringe of isotonic saline intravenously immediately before induction of anaesthesia to ensure the blindness of the anaesthetist.

Results: Gabapentin and midazolam offered management of PONV for parturients just like the control drug (Granisetron) with no statistically significance between the three groups (p-value >0.2). Regarding pain Gabapentin offered analgesia all through the postoperative 8 hours by significant difference (p-value<0.02) among the three groups compared to the midazolam which was a statistically significant at only 4 hours postoperatively (p-value=0.01) but the two drugs gave the same results in decreasing the analgesic requirements all through the postoperative period as the total number of rescue analgesic doses was statistically significant between the two groups and the control group (p-value=0.0001). Regarding amnesia Midazolam was distinct with high significant difference (p-value=0.0001) in offering amnesia compared to the two other groups which offered no amnestic effects. In contrast there was no significant difference among the three groups between sedation using Ramsay sedation score (p-value>0.1) and neonatal wellbeing using Apgar score (p-value>0.3).

Conclusion: Gabapentin (600mg) and Midazolam (20 ug/kg) are safe and efficient in decreasing (PONV), pain scores and analgesic requirements without any sedative effects on the parturient or negative effects on neonatal well-being.

Key words: Gabapentin, Midazolam, Granisetron, postoperative nausea, vomiting, C.S.