Annals of Medicine and Surgery 77 (2022) 103570

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Cross-sectional Study

Effect of low-dose intravenous ketamine on postoperative pain following cesarean section under spinal anesthesia: A prospective cohort study, Ethiopia

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ARTICLE INFO

Keywords:
Cesarean section
Spinal anesthesia, low-dose intravenous ketamine
Postoperative pain
Post-operative analgesia consumption

ABSTRACT

Background: Following cesarean delivery, mothers experience moderate to severe pain since postoperative analgesia of spinal anesthesia is limited by duration of local anesthetic agents used. Analgesic effect of local anesthetic agents could be extended and supported by adding either intravenous or intrathecal adjuvants. The primary outcome of this study is to assess effect of low-dose intravenous ketamine on postoperative pain following cesarean section under spinal anesthesia.

Materials and methods: This prospective observational cohort study recruits 60 parturients who underwent elective cesarean delivery under spinal anesthesia. Those parturients who received intravenous ketamine 0.25 mg/kg following spinal anesthesia were considered as exposed group/ketamine group. The Non-exposed group was those parturients who didn't receive intravenous ketamine following spinal anesthesia. Numerical rating scale pain score, time to request first analgesia and total analgesia consumptions were recorded starting from 1st hour to 24 h after the end of surgery.

Results: The median and Inter quartile range (IQR) for postoperative numerical rating scale pain score was significantly higher in non-exposed group compered to ketamine group at 1st and 2nd hour after operation (P-value<0.05). Time to request first analgesia was significantly longer in ketamine group [192.5(140–210) minutes] compared to non-Exposed group [146(130–160) minutes] with P-value < 0.001. Tramadol consumption within 24 h postoperatively were significantly lower in ketamine group compared to non-exposed group (P-value < 0.001).

Conclusion: Low dose intravenous ketamine before skin incision was extended postoperative first analgesia request time by average of 45.5 min and decrease total analgesia consumption in 24 h.

1. Introduction

Cesarean delivery is widely done obstetric surgery; When done with medical indication is a lifesaving operation and play important role in decreasing maternal mortality [1,2].

Even though WHO recommend rate of cesarean section were between 10% and 15%; Cesarean delivery rate is progressively increased in both developed and developing country [2,3]. Reason for rising of cesarean delivery rate is concept of cesarean delivery as safe procedure; Despite of health-related risk and financial crisis [1]. Cesarean section can negatively affect mothers' physical, psychological, social and environmental life quality after delivery and post operation pain is the common adverse event after cesarean delivery [4].

Postoperative pain intensity can be affected by some factors such as preoperative pain, depression, preoperative anxiety, type of anesthesia, analgesics and time of surgery were some factors [5,6]. Pain following cesarean section has many complications such as respiratory insufficiency, cardiac complication, coagulation problems, urine retention and delaying gastric emptying [7–9].

Postoperative pain prevention and shortening in bed duration of the parturient and supporting to ambulate as fast as possible after the operation reduce the general complications [8]. There are different medications to reduce postoperative pain. Depend on patient's preference, health profession select the most suitable drugs for each patient. Most of health institutions use narcotics for controlling post cesarean section pain. However, narcotics have many adverse events such as respiratory depression, addiction, drug adaptation, nausea, and

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https://doi.org/10.1016/j.amsu.2022.103570
Received 16 February 2022; Received in revised form 28 March 2022; Accepted 31 March 2022
Available online 3 April 2022

Abbreviations

ASA	American Society of Anesthesiologists
CD	Cesarean Delivery
C/S	Cesarean Section
Hr	Hour
IQR	Interquartile Range
MAP	Mean Atrial Pressure
MD	Mean Difference
Mg	Milligram
NMDA	*N*-Methyl D Aspartate
NRS	Numeric Pain Rating Scale
PCA	Patient Controlled Analgesia
PONV	Postoperative Nausea and Vomiting
SA	Spinal Anesthesia
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
VAS	Visual Analogue Scale
WMD	Weighted Mean Difference
WHO	World Health Organization

vomiting [3,8,10,11]. So, health profession generally chooses non-narcotics analgesics for decreasing post-surgery pain.

Uncontrolled pain causes persistent nociceptive and neuropathic pain which patients feel and opioid-induced hyperalgesia partially mediated through *N*-methyl-D-aspartate (NMDA) receptors [12]. Many researches have explored the effect of sub-anesthetic dose of ketamine together with other drugs in decreasing post-surgery pain [8,13]. Sub-anesthetic dose of ketamine can antagonize the NMDA receptor-mediated pain sensitization [14,15].

Many researchers reported function of *N*-methyl-D-aspartate (NMDA) receptor in nociceptive pathway and pain processing, such as central plasticity, increasing pain severity and decrease pain threshold [16,17]. Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor inhibitor that causes analgesia by desensitization of stimulated *N*-methyl-D-aspartate receptor, so by blocking pain signal in central nerve system [18,19].

Low-dose ketamine also decline the activity of brain structures that respond to noxious stimuli [14]. It has effects on opioid receptors and stimulates monoaminergic descending inhibitory pathways at supra-spinal sites causing in antinociception, all of which mediate analgesic effects [14,20–22].

Hence, the primary outcome of this study is to compare post-operative numerical rating scale pain score among partiruents taking ketamine before skin incision and does not take ketamine before skin incision after spinal anesthesia. The secondary outcomes are to compare first analgesia requestion time between the groups and to compare total 24-h analgesia consumption between Exposed and Non-exposed groups.

2. Materials and Methods

2.1. Research registration

Unique Identifying number or registration ID: Research registry 7623 'retrospectively registered' [23].

Ethical approval

Institutional review board of Addis Ababa University, College of Health Science approved the study and Ethical clearance was obtained from Addis Ababa University, College of Health Science ethical clearance committee before the start of the study. This study was conducted in Empress Zewditu Memorial Hospitals, one of the public hospitals which was affiliated by Addis Ababa university, College of Health Science in Addis Ababa, capital of Ethiopia.

Study design: Institution based comparative observational cohort study was conducted from February 1, 2021 to April 30, 2021.

Source population: All pregnant mothers who were give birth by elective caesarian section under spinal anesthesia at Empress Zewditu memorial Hospital.

Study population: All eligible pregnant mothers who underwent elective caesarian delivery under spinal anesthesia in the study period.

Inclusion criteria: ASA II parturients and single (not twins) term pregnancy.

Exclusion criteria: ketamine allergy, changes in anesthesia, high blood pressure, high intracranial pressure, history of seizure, number of spinal anesthesia attempt above one, patients took other pre or intra-operative analgesia.

Sample size and sampling technique: Time to first analgesia request was one of outcome indicators and we take previous observational study [24] which reported Time to first analgesia request (hour) in Exposed 4.22 ± 2.6 and non-exposed group 2.33 ± 2.2. By assuming 1:1 ratio, the sample size was determined by the formula as,

$$n1 = n2 = (\sigma 12 + \sigma 22)\,(Z\alpha/2 + Z\beta)2$$

$$(\mu 1 - \mu 2)2$$

$$\text{Where } n = (2.62 + 2.22)\,(1.96 + 0.84)2$$

$$(4.22–2.33)2$$

$$= (11.6) \qquad (7.84)$$

$$(1.81)2$$

$$= 91/ \qquad 3.28$$

$$n1 = n2 = 27.74 \qquad \approx 28$$

Ten percent of additional sample was included by assuming loss to follow up and a total of 30 samples for each group were calculated N = 62 patients.

Where; N = total sample size

n1 = number of partriuents under spinal anesthesia ketamine exposed group

n2 = number of partriuents under spinal anesthesia non-exposed group.

Z = 95% confidence interval = 1.96.

$1\text{-}\beta$ = the power function at 80% = 0.84

σ1 – Standard deviation for time to first analgesia request of ketamine group

σ2 - Standard deviation for time to first analgesia request control group

μ1 - Mean for first analgesia request ketamine group

μ2 - Mean for first analgesia request control group.

2.2. Procedural details

During the study period 114 parturients were estimated to undergo elective Cesarean section procedure under spinal anesthesia in the hospital. With systematic random sampling every 2nd parturients who were scheduled for Cesarean section under spinal anesthesia, fulfill inclusion criteria and volunteer were recruited to take part in the study. "Since randomized control trial (RCT) was not yet allowed in our university, the patients were not randomized for anesthetic management; Rather by starting at random, every selected participant was placed to either group based on the responsible anesthetist's post-operative pain management plan [25]" (whether they received low-dose intravenous ketamine before skin incision or not). Those parturients who received low-dose intravenous ketamine 0.25 mg/kg before skin incision were considered as Exposed. The responsible anesthetist to administer anesthesia take anesthesia consent and if administering a ketamine is his/her

plan for post operative pain management he/she also take verbal consent for ketamine administration. The Non-exposed group was defined, in this study, as those parturients who didn't receive low-dose intravenous ketamine before skin incision. This continues until the desired sample in each group were achieved. The outcomes were assessed by trained ward nurses.

Parturients were given training and instructed on how to self-report pain using the eleven Point Numeric Rating Scale (NRS) score 0 to 10 in the morning of operation day at the ward with trained nurse [25]. Participant's involvement in the study was on voluntary bases, participants who were not willing to participate in the study & those who wish to quit their participation at any stage was informed verbally to do so without any restriction.

Numeric rate scale (NRS) pain score and other variables were documented at 1st hour, 2nd hour, 6th hour, 12th hour, 18th hour and 24th hours of post operative period after the end of procedure. A time in minutes from end of procedure to first analgesia request were documented together with total analgesia (opioid) consumption in the first 24 h. Data were checked for completeness, accuracy and clarity by the investigators.

2.3. Data processing, analysis and report

Data was coded, edited and then entered and cleaned using Epi Info version 7 and exported and analyzed using Statistical package for Social Sciences (SPSS) software version 26.0. Shapiro Wilk test were used to test for distributions of data while homogeneity of variance was assessed using Levene's test for equality of variance. Numeric data were described in terms of mean ± SD for symmetric and median (Interquartile range) for asymmetric data respectively. Comparisons of numerical variables between study groups were done using unpaired student t-test (independent t-test) for symmetric data and Manny Whitney *U* test were used for asymmetric data. Frequency and percentage were used to describe categorical variable and statistical difference between groups were tested using Chi square or Fisher's exact test, as appropriate. Significance was determined at P value < 0.05.

The work has been reported in line with strengthening the reporting of cohort studies in surgery (STROCSS) criteria [26].

Operational Definition: the following definitions were used for this study.

Adverse event: unwanted effect that happen secondary to administration of a drug.

Analgesia: any group of drugs used to relief pain.

ASA classification: American Society of Anesthesiologists classification of patient physical status based on presence or absence coexisting diseases and limitation activity to predict morbidity and mortality of the patients.

Baseline vital sign: vital sign taken before spinal anesthesia delivery.

Duration of surgery: Time from start of skin incision to end the operation.

Exposed group: participants who were take 0.25 mg/kg iv ketamine after spinal anesthesia.

Hallucination: perception of something present in the absence of real stimulus [16].

Hypotension: when systolic blood pressure less than 90mmhg or decreased MAP by greater than 20% from baseline [18].

Hypertension: Systolic blood pressure elevation of at least 20% of the preoperative value that persists for longer than 15 min [27].

Non-exposed: participants who did not take 0.25 mg/kg iv ketamine after spinal anesthesia.

Numeric Rating Scale: pain severity assessment tool that patients report their pain by rating from 0 to 10 (11point scale) with assuming that 0 shows no pain and 10 shows the most unexplained pain [28].

Premedication: medication given before induction of anesthesia for different purpose.

Procedure: cesarean section surgery.

RAMSAY Sedation scale: Sedation level monitoring for patients take sedative drug [29].

Spinal Anesthesia: Injection of local anesthetic into the cerebrospinal fluid in the spinal canal to block sensory and motor sensations before they reach the central nervous system. It is used mainly during surgery on the lower abdomen and legs.

Time to First Analgesia Request: A time in minutes from spinal anesthesia given to first time patient request for analgesia.

Total Analgesia Consumption: Total dose of painkiller given in mg within the first 24hr post-surgery.

Vomiting: Expelling of ingested food through the mouth after spinal anesthesia deliver to the first 24hrs of operation.

3. Results

3.1. Demographic and preoperative clinical characteristics

A total of 60 parturients (30 in each group) were analyzed based on whether they received low-dose intravenous ketamine or not with response of 97%. One patient data from each group was excluded due to incomplete data from non-exposed and lost follow up from Exposed group. There was no statistically significant difference between the two groups in demographic and pre-operative clinical characteristics such as age, weight, height, BMI, base line vital sign, parity and previous cesarean section ($P > 0.05$) as shown in Table 1.

3.2. Anesthesia and surgery characteristics

All parturients in both groups premedicated with 10 mg intravenous metoclopramides. Preloaded fluid volume was similar for both exposed and non-exposed groups. No significant deference in lumbar puncture site, spinal needle gauge, intraoperative fluid given and blood loss between both exposed and non-exposed Table 2.

3.3. Comparison of postoperative pain severity by numeric pain rating scale

The Mann Whitney *U* test showed that the median NRS score were lower in the Exposed group at 1st and 2nd hours postoperatively ($P < 0.05$) as shown in Table 3. There were no statistically significant difference results at 6th, 12th, 18th and 24th hours post-surgery between the two group with P-value >0.05 as shown in Table 3.

Comparison of Time to First Analgesia Request and Total Analgesia

Table 1
Demographic and Pre-operative clinical characteristics of parturients who undergo elective caesarian section procedures under spinal anesthesia.

Variables	Exposed group n = 30	Non-exposed group n = 30	P value
Age in year (mean ± SD)	29.63 ± 5.611	29.43 ± 4.272	.877
Weight(kg) (mean ± SD)	70.33 ± 6.48	72.03 ± 6.78	.325
Height(cm) (mean ± SD)	165 ± 0.06	167 ± 0.05	.301
BMI (mean ± SD)	25.47 ± 1.77	25.87 ± 1.97	.414
Parity (median (IQR))	2(0_3)	2(0–4)	.905
No. previous c/s (median (IQR))	1(0_3)	1(0_3)	.562
educational status: read and write n(%)	8(26.67%) 15(50%)	11(36.67%) 14(46.67%)	.766
- diploma n (%)	7(23.30%)	5(16.67%)	
- degree n (%)			
Base line HR (mean ± SD)	84.87 ± 6.892	86.10 ± 6.326	.473
Base line MAP (mean ± SD)	79.40 ± 4.288	78.5 ± 4.876	.451

Abbreviations: n (%)- frequency (percent), Kg-kilogram, cm-centimeter, BMI-body mass index, No-number, ASA-American society of anesthesiologist, HR-heart rate, MAP-mean arterial pressure, SD−standard deviation, IQR-inter quartile range.

Table 2
Anesthesia and surgery characteristics of parturients who undergo elective caesarian section procedures under spinal anesthesia.

Variables	Exposed group n = 30	Non-exposed group n = 30	P-value
Premedication: metoclopramide 10 mg iv	30(100%)	30(100%)	
Preload fluid median (IQR) in (ml)	600(400–800)	600(500–800)	.563
Site of LP. b/n L3/4 n (%)	9(30%)	7(23.3%)	.559
L4/5 n (%)	21(70%)	23(76.7%)	
Spinal needle gauge 24	100%	100%	
Bupivacaine: isobaric (0.5%)	100%	100%	
Volume (12.5 ml)	100%	100%	
Intraoperative fluid given median (IQR) in ml	2000 (1800–2400)	2000(2000–2500)	.284
Intraoperative blood loss	325(300–500)	325(250–500)	.419
Duration of operation (minute)	33.77 ± 0.589	34.67 ± 0.611	.293

Abbreviations: IQR-Inter quartile range, no (%) Frequency (percentage): independent sample t-test, Mann Whitney test and chi-square tests was used, p-value < 0.05 taken as significant.

Table 3
Comparison of postoperative pain severity using NRS score (0-10) between Exposed and Non-exposed group.

Variables expressed as median (IQR)	Exposed group n = 30	Non-exposed group n = 30	p-value
Postop. NRS at 1st hr.	0	0(0_1)	.040
Postop. NRS at 2nd hr.	0	2(0_3)	.000
Postop. NRS at 6th hr.	3(1_5)	3(1_6)	.326
Postop. NRS at 12th hr.	4(1_6)	4(2_6)	.642
Postop. NRS at 18th hr.	2(1_4)	2(1_4)	.395
Postop. NRS at 24th hr.	2(1_3)	2(1_4)	.569

Abbreviations: IQR- Interquartile range, hr. - hour, NRS- Numerical pain rating scale.

Consumption between Groups.

The Mann Whitney *U* test showed that the median time to first analgesia request in minutes were longer in Exposed group with 192.5 min compared to median time of 146 min in the non-Exposed group (P-value <0.001). There was also statistically significant difference with regard to median Tramadol consumption within 24 h between the two group with P-value <0.001 as shown in Table 4.

4. Discussion

Numeric rating scale is regularly favored in clinical setting for pain scale measurement due to their simple administration, relatively consistent result and its correlation with that of VAS [30]. NRS and VAS equally effective and interchangeably used for assessment of post-operative pain [31]. This study showed that at 1st post-operative time the median postoperative pain score (NRS) was 0 in exposed group and 0 (0–1) in non-exposed group ($p < 0.05$). The comparison also shows lower median pain score 0 in exposed group compared to 2(0–3) in non-exposed group at 2nd post-operative time ($p < 0.001$). There was no statistically significant different result at 6th, 12th, 18th and 24th hours between the two groups.

Table 4
Comparison of time to first analgesia request in minutes and total analgesia consumption in milligram between Exposed & non-Exposed groups at Empress Zewditu memorial Hospital, Ethiopia.

Variable Expressed as median (IQR)	Exposed group n = 30	Non-exposed group n = 30	p-value
First time request for analgesia in (minute)	192.5(140_210)	146(130_160)	< .0001
Postoperative analgesic consumption	100(100_100)	150(100_150)	< .0001
Tramadol iv in mg	75(75_150)	75(75_150)	.576
Diclofenac im in mg			

Abbreviations: im-intramuscular, iv-intravenous, mg-milligram, IQR-inter-quartile range.

Our finding is in line with Prospective RCT study done in Istanbul (Turkey) 2005. According to this study VNRS values at first post-operative hour after operation in the non-exposed group (2.4 ± 0.8) were found to be significantly higher than those of in exposed group (0) ($p < 0.05$). According to the same study VNRS values of non-exposed group (3.1 ± 1.0) at 2nd post-operative hour were found to be significantly higher than those of in exposed group (1.4 ± 0.8) ($p < 0.05$) [21]. Comparable results were also reported in the study done in Nigeria (2012) with statistically significant higher value of Visual Analogue Score (VAS) scores in non-exposed group compared to exposed group at 1st and 2nd hours after operation [20].

In contrary to our result study done in Iran, 2011 reported that postoperative visual analogue scale pain score was not significantly difference between ketamine and control groups in first 24 h [32]. This difference may due to ketamine doses difference in our study anesthetists used 0.25 kg/mg while they used 0.15 mg/kg, study design and sample size difference (60 vs 120).

According to our study the median time to first analgesia request in minutes were longer with median and IQR of 192.5(140–210) minutes in Exposed group compared to 146(130–160) minutes in non-Exposed group ($p < 0.001$). This may increase satisfaction level of parturients, decrease post operative analgesia consumptions as request time elapsed and avoid side effect of multiple drug consumption in immediate post operative period. In line with our result, study done in Uganda, 2017 showed that median (range) time (in minutes) to first analgesia request was Significantly longer in the ketamine group [210 (90–270)] than control group [180 (90–360)] [33]. Similarly, RCT done in Nigeria, 2012 match with our study result that showed first analgesia request time was significantly higher in ketamine group(209 ± 14.7min) than control group (164 ± 14.1) [20].

Also, study done in Turkey, 2005 match with our finding that showed time to first request for analgesia was significantly longer in the ketamine (197 min) compared to the control group (144 min) [21]. In contrary to our result, study done in Iran, 2014 showed time to analgesic request was 5.8 (3.6) hr. in ketamine and 6 (5.5) hr. in the control group which was not significant difference between the groups [10]. The difference may secondary to difference between doses of ketamine, in our study anesthetists used 0.25 mg/kg while they used 0.2 mg/kg and different study design. Another study conducted in Chicago, 2011 was also not in line with our study that showed time to the first analgesia request was 684 (337, 1031) minutes in ketamine group and 760 (346, 1174) minutes in control group that was not significant difference between groups [19]. The difference may due to ketamine doses difference, time of injection ketamine injection, in our study bupivacaine was used alone for spinal anesthesia while they used additive 15 μg fentanyl, also sample size difference (60 patients vs. 188patients).

The result of this study showed the median and inter-quartile Tramadol consumption with in 24 h was significantly higher in non-exposed group 150(100–150) compare to exposed group 100(100-100) in milligram. This finding was in line with study done in Nigeria (2011) that reported the total tramadol consumption in first 24hrs 84.0 ± 9.76 mg in ketamine group and 106.5 ± 7.16 3.68 mg in control group that was significant [34]. Another study conducted in Iran, 2002 also match with our study result, morphine consumption in 24 h was lower in the ketamine group (6.25 ± 3.42 mg) than in the control group (17.73 ± 4.08) in mg [35].

In Contrast to our study finding, study conducted in Uganda, 2017 showed diclofenac consumption was significantly lower in ketamine 75 (75–150) than control group 150 (75–150) in mg, but, total tramadol consumption was not significant [33]. This difference may due to pain control protocol difference, study design and sample size. Study

conducted in Korea university of Soonchunhyang, 2013 also not in line with our result that report total analgesia consumption was not difference between ketamine and control group [36]. This may due to pain management protocol difference in their study area fentanyl and ketorolac while in our study hospital tramadol then diclofenac was pain management protocol. The main limitation of this study includes that the study was not randomized and the plane to give or not give ketamine was on discretion of respective anesthetist who administer spinal anesthesia.

4.1. Strength and limitation of the study

4.1.1. Strengths of the study

Study groups were homogenous (elective pregnant mothers). We used exclusion criteria to prevent cofounding and groups are comparable in terms of socio demographic distribution and perioperative factors; the difference observed might be secondary to the exposure factor.

4.1.2. Limitation of the study

This study lack of control on some factors like time between operation end to recovery time and spinal anesthesia injection rate by different anesthetists. Since randomized control trial is not allowed in our institution, we cannot randomize the study.

4.1.3. Relevance and implications

It is clinically relevant particularly in the settings like ours, where resources are limited and post operative pain managements are challenging. It gives implication for further researcher.

5. Conclusion

The findings of our study demonstrate that low dose intravenous ketamine (0.25 mg/kg) following spinal anesthesia before skin incision decrease 1st and 2nd hour pain severity after operation with extended postoperative time to request first analgesia by average of 45.5 min and reduce total analgesia consumption in first 24hr.

Research registration number

Research registry 7623.

Availability of data and material

The data used in this study was collected by trained data collectors and authors are willing to share the data upon request from peer researchers.

Provenance and peer review

Not commissioned externally peer reviewed.
The authors have no conflicts of interest to declare.

Ethical approval

Institutional review board of Addis Ababa University, College of Health Science had given approval for the study and Ethical clearance was obtained from Addis Ababa University, College of Health Science ethical clearance committee before the start of the study. Reference. Meeting No. 125/2021, protocol number: Anes 11/13, Assigned No. November 2021.

Funding

This work was funded by Addis Ababa University.

The study sponsors have no role in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Author contribution

Hirbo Samuel: This author helped on substantial intellectual contributions to conception, design, and acquisition of data, analysis, and interpretation of data as well as on preparing the manuscript to this study. **Senait Aweke**: has been involved in analysis, interpretation of data and drafting the manuscript and revising it critically for important intellectual contents. **Jemal Tuni:** This author contributed to conception, design, analysis and interpretation of data and give approval of the final version to be published.

Consent

Written informed consent was obtained from the patient for publication of this observational study. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of Research Studies

1. Name of the registry: research registry.com
2. Unique Identifying number or registration ID: Research registry 7623
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com

Guarantor

Hirbo Samuel.
Jemal Tuni.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgements

we would like to thank Addis Ababa University College of Medicine and Health Science for funding this research. Our gratitude goes to supervisors, data collectors and study respondents. Finally, we would like to thank all those, who in one way or another have contributed in this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103570.

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