Effectiveness of Intrathecal Dexmedetomidine as an Adjuvant to Bupivacaine for Infants Undergoing Infra-Umbilical Surgeries: A Dose Response Study

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Abstract

Introduction: Administration of optimum anesthesia in infants undergoing surgeries is challenging. There is a debate over the cost and benefits of each used anesthetic agent in the literature. In this study, we aimed at identification of the optimum dose of dexmedetomidine as an adjuvant to Bupivacaine for Infants undergoing infra-umbilical surgeries.

Methods: In a comparative randomized controlled trial, we included 92 infants who underwent infra-umbilical surgeries. Patients were divided into four groups according to the received anesthesia. Group 1 received spinal anesthesia with bupivacaine 0.5% only; group 2 received Dexmedetomidine 0.25 µg/kg as an adjuvant to bupivacaine 0.5%; group 3 received Dexmedetomidine 0.3 µg/kg as an adjuvant to bupivacaine 0.5%; group 4 received Dexmedetomidine 0.4 µg/kg as an adjuvant to bupivacaine 0.5%. We assessed onset and duration of sensory and motor block, postoperative pain, and postoperative need for rescue analgesia.

Results: A dose of 0.3 µg/kg dexmedetomidine in addition to bupivacaine was associated with the best outcomes regarding level of sedation, and postoperative pain scores.

Conclusions: Dexmedetomidine is a good adjuvant to bupivacaine in infants surgeries; specifically the dose of 0.3 µg/kg.

Keywords: Dexmedetomidine, Infra-Umbilical Surgeries, Bupivacaine, spinal anesthesia.

DOI Number: 10.48047/nq.2024.22.2.NQ24034 **NeuroQuantology 2024; 22(2):330-339**

Introduction:

Safe and effective anesthesia care of pediatric patients specially neonates and infants for surgery. Anesthesia for pediatric patents demands a systematic understanding of the rapidly changing physiology of the patients, the pathology of the coexisting diseases and both the pharmacokinetics and the pharmacodynamics of the medications used to deliver the anesthesia (1).

Nowadays, spinal anesthesia (SA) is used in infants and children for different types of surgery of lower part of body. It can be used as a sole technique with or without sedation or in conjunction with general anesthesia (GA) in complex surgery in light of growing concerns in popular media regarding neurotoxicity of anesthetics (2).

SA is advantageous in that it uses small dose of anesthetic, is easy to perform and offers a rapid onset, reliable surgical analgesia and good muscle relaxation with high success rate (2).

Advantages sometime offset by a relatively short duration of action and complaints of postoperative pain when it wears off. Hyperbaric local anesthetics (LA) are commonly used as they produce more predictable block (3).

Bupivacaine is a potent LA with long duration of action. Bupivacaine can obstruct the inward flow of sodium ions through the nerve membrane thus

preventing the generation of action potential; this action starts within 2-10 minutes. SA with hyperbaric bupivacaine hydrochloride is popular for longer procedure due to its prolonged duration but there is a need to intensify and increase the duration of sensory block and thus prolongs the duration of postoperative analgesia (4).

Besides failure of lumbar puncture, the relatively short duration of action and exceedingly variable characteristics between individuals (such as duration on anesthetic, analgesic and motor actions) are among the major limitations of single-injection SA. Up to 45% of patients under SA need sedative or anesthetic agents to complete surgery, which in turn negates the benefit of SA. The addition of different types of adjuvant modifies the onset time, efficacy and duration of spinal block (5).

The addition of dexmedetomidine, selective centrally acting Alpha 2 agonist, as an adjuvant to intrathecal LAs in adults is associated with earlier, prolonged sensory block characteristics and later need for analgesic requirements. The major advantages of this drug is the lack of respiratory depression, pruritus, nausea, and vomiting which are opioid-related side effects(6), in addition toimproving the quality of sensory and motor blockade (7,8).

Although, intrathecal dexmedetomidine produces dose dependent analgesia in adults, the dose of spinal dexmedetomidine has not been investigated in infants

Aim of study

This study was conducted to provide a good operating condition for the surgeon and to choose the appropriate type of anesthesia and drug doses with the minimal side effects and good postoperative analgesia for infant patients.

Patients and Methods

In a randomized double Blinded controlled study, we included 92 infants undergoing elective minor or medium infra-umbilical surgeries at Suez Canal University Hospitals. Included participants were infants aging 29 days to 12 months with physical status American society of anesthesiologists I or II (ASA I or ASA II). We excluded infants with gestational age less than 37 weeks; obese infants, whose BMI at or above the 95th percentile for children of the same age and sex; with known history of allergy to the used drugs; have contraindications of spinal anesthesia; with neurological diseases (multiple sclerosis, increased intracranial pressure, demyelinating lesions); or with spinal deformity (such as scoliosis). Approval from Research Ethics Committee of Faculty of Medicine Suez Canal University was obtained before starting our study. An informed consent was taken from parents of all participants before taking any data or doing any procedure.

Randomization, blinding and allocation concealment

Patients were randomly assigned into four equal groups using a randomization computer program. Randomization sequence was concealed in opaque numbered envelops that had been opened on day of surgery to show the group assignment. Group (1) control group: received spinal anesthesia with bupivacaine 0.5% only (bupivacaine 0.5% was given at a dose of 0.5 mg/kg for infants weighing less than 5kg and 0.4 mg/kg for those weighing >5kg); group (2): received Dexmedetomidine 0.25µg/kg as an adjuvant to bupivacaine 0.5%; group (3): received Dexmedetomidine 0.3µg/kg as an adjuvant to bupivacaine 0.5%; group (4): received

Dexmedetomidine 0.4µg/kg as an adjuvant to bupivacaine 0.5%. Dexmedetomidine dose was prepared by adding 100 µg of dexmedetomidine to 20 ml vial of isobaric bupivacaine 0.5%, so that every 1 ml isobaricbupivacaine 0.5% contained 5 µg of dexmedetomidine. The calculated dose of dexmedetomidinein each group was added to hyperbaric bupivacaine 0.5%by insulin syringe and deducted from the total volume given.

Anesthetic technique

All patients were pre-medicated 30 minutes before the procedure with: Midazolam 0.5 mg/kg orally by syringe, Atropine 0.02 mg/kg IM and EMLA ™ cream, 0.5-1ml applied to the lumber and sacral region. Patients were positioned in lateral position with head extension and hip flexion. Then full aseptic precautions were followed. Lumbar puncture was done in one of these levels (L4-L5 or L5-S1) by midline approach, using 25G Quincke spinal needles. Patients were put in supine position with head elevation immediately after injection till the level had been stabilized.

Outcome measures

- The level of sensory block was determined by attempting to elicit a grimace to bilateral firm skin pinch at each dermatome every 2 minutes. The operation was allowed to begin after both lower limbs became flaccid.
- The motor block was assessed by observation of the lower limb movement using modified Bromage scale: 0 = full motor strength (flexion of knees and feet), 1 = flexion of knees, 2 = little feet movement, 3 = no movement of knees or feet.
- Postoperative pain was assessed using FLACC (Face, Leg activity, Arm activity, Cry, and Consolability) scores after 30 minutes, 1 hour, 2 hours and 4 hours after the surgery.
- Postoperative rescue analgesic administration consisted of paracetamol 15 mg/kg I.V for pain scores > 3 every four to six hours, with a maximum of 60 mg/kg daily and fentanyl 0.5µg/kg I.V for pain scores > 5. The total doses of rescue analgesics in the postoperative period were recorded.

Statistical analysis was performed using a Statistical Package for the Social Sciences SPSS® version 25. Descriptive data was expressed as mean and SD for continuous variables, and count and/or percentages (%) for dichotomous variables. One-way analysis of variance (ANOVA) was used to analyze continuous variables between the four groups, while discrete (categorical) variables were analyzed using the Chi-square. The level of statistical significance was considered to be $p<0.05$.

Results

In this study, 100 patients were included who underwent elective minor infraumbilical surgeries. Twenty three patients in each group, and eight patients were excluded during the study due to failed spinal technique (n=5), and inadequate spinal block (n=3), all were converted to general anesthesia.

The patients' age distribution was around 6 months. The number of males was higher than females. Their mean weight was about 5-6 Kg. All of these data showed no statistically significant difference between the four groups (Table 1).

There was a higher incidence of certain surgeries between the four groups such as unilateral inguinal hernia which was performed in over one fourth of the patients. The least common surgery among all groups was Achilles tenotomy. Overall, there was no statistically significant difference in the frequency of specific operations between the four groups or in the

mean duration of surgery. The mean duration of all surgeries was approximately 45 minutes in all the four groups (Table 2).

The majority of patients received spinal anesthesia between L4-5 as it was the best surface anatomy felt in the lateral position. In addition, most of the patients were punctured once; few patients had two trials due to difficulties in spinal technique or patient position. Generally, there was no statistically significant difference in the puncture level and number of skin punctures among the studied groups (Table 3).

The onset of sensory block was around 2.6 minutes among the four groups, while the onset of motor block was around 3 minutes. The duration of sensory block was variable between the studied groups with the least duration witnessed in group 1 (64 minutes), and the longest duration was in group 4 (163 minutes). Similarly, the duration of motor block was asymmetrical. The least duration was 43 minutes in group 1, and the longest duration was (131 minutes) in group 4. Within the spinal characteristics, only the duration of sensory and motor blockade had a statistical significant difference between the studied groups, with group 4 was higher than other groups (Table 4).

Regarding the intraoperative sedation level, all patients were either drowsy or mildly sedated. The majority of patients were mildly sedated; but, most of the patients in group 1 were drowsy. The number of patients needed rescue analgesia in group 1 was statistically significant higher compared to group 3 and 4. When it came to the first time to request analgesia, group 4 had a significantly longer duration of postoperative analgesia (163 minutes) than the other three groups, while group 1 was the earliest to need analgesics by (64 minutes) (Table 5).

Concerning postoperative FLACC scores, after 30 minutes, the majority of patients in groups 2, 3, 4 experienced mild discomfort, while all patients from group 1 witnessed moderate pain. After 1 hour, the majority of patients in all groups had mild discomfort. By 2 hours, around two thirds of patients in groups 3 and 4 become more relaxed and comfortable, while two thirds of patients in groups 1 and 2 were still feeling mild discomfort. Similarly by 4 hours, approximately more than 60% of all patients felt relaxed and comfortable. Overall, during the first 2 hours postoperative, group 4 was the least to suffer from pain, while group 1 was the most affected group. After 4 hours, there was no statistical significant difference between the four groups (Table 6). There was a statistically significant difference in FLACC scores after 30minutes between group 1 and each of groups 2, 3, and 4, in addition to group 2 versus group 4. After 1 hour, there was a statistically significant difference between group 1 and each of groups 2, 3, and 4. After 2 hours, there was a statistically significant difference between group 2 and each of groups 3 and 4 only (Table 7).

Table 1: Demographic data of patients

		Group 1 (n = 23)	Group 2 (n = 23)	Group 3 (n = 23)	Group 4 (n = 23)	P value
Age (months)		5.74 ± 2.6	6.65 ± 2.4	6.17 ± 2.75	6.91 ± 2.55	0.435
Sex	**Male**	13 (56.5%)	12 (52.2%)	14 (60.9%)	13 (56.5%)	0.950
	Female	10 (43.5%)	11 (47.8%)	9 (39.1%)	10 (43.5%)	
Weight (kg)		5.73 ± 1.39	5.71 ± 1.45	5.37 ± 1.41	6.02 ± 1.57	0.369

Data are presented as mean ± SD and frequency (%)

Table 2: Types and duration of surgeries.

	Group 1 (n=23)	**Group 2 (n=23)**	**Group 3 (n=23)**	**Group 4 (n=23)**	**P value**
Types of Surgeries					
Unilateral inguinal hernia	6 (26.1%)	9 (39.1%)	10 (43.5%)	10 (43.5%)	0.97
Bilateral inguinal hernia	3 (13.0%)	4 (17.4%)	1 (4.3%)	3 (13.0%)	
Unilateral DDH	3 (13.0%)	2 (8.7%)	2 (8.7%)	2 (8.7%)	
Undescended testis	4(17.4%)	3 (13.0%)	2 (8.7%)	2 (8.7%)	
Colostomy closure	4 (17.4%)	3 (13.0%)	6 (26.1%)	5 (21.7%)	
Achilles tenotomy	3 (13.0%)	2 (8.7%)	2 (8.7%)	1 (4.3%)	
Duration of surgeries (min)	45.65 ± 11.7	44.78 ± 10.2	42.17 ± 8.5	43.04 ± 10.0	0.06

Data are presented as frequency (%) DDH: developmental dysplasia of the hip

Table3: Spinal technique characteristics.

	Group 1 (n=23)	**Group 2 (n=23)**	**Group 3 (n=23)**	**Group 4 (n=23)**	**P value**
Puncture level					
L4-L5	16 (69.6%)	15 (65.2%)	15 (65.2%)	16 (69.6%)	0.97
L5-S1	7 (30.4%)	8 (34.8%)	8 (34.8%)	7 (30.4%)	
No. of skin punctures (Trials)					
Once	19 (82.6%)	17 (73.9%)	20 (87.0%)	19 (82.6%)	0.71
Twice	4 (17.4%)	6 (26.1%)	3 (13.0%)	4 (17.4%)	

Data are presented as frequency (%)

Table 4: Onset and duration of spinal blockade.

Variable	**Group 1 (n=23)**	**Group 2 (n=23)**	**Group 3 (n=23)**	**Group 4 (n=23)**	**P value**
Onset of sensory blockade	2.96 ± 1.06	2.78 ± 0.95	2.61 ± 0.72	2.65 ± 0.77	0.54
Onset of motor blockade	3.00 ± 0.95	3.34 ± 1.15	3.52 ± 0.99	3.04 ± 0.82	0.22
Duration of sensory blockade	64.78 ± 9.22	98.48 ± 8.97	123.48 ± 7.75	163.04 ±14.51	0.000*
Duration of motor blockade	43.26 ± 2.43	71.96 ± 5.58	99.35 ± 6.95	131.52 ± 8.58	0.000*

Data are presented as mean ± SD and frequency (%)

Table 5: Intraoperative sedation and analgesia.

	Group 1 (n=23)	Group 2 (n=23)	Group 3 (n=23)	Group 4 (n=23)	P value
Intraoperative sedation level					
Alert	0 (0)	0 (0)	0 (0)	0 (0)	0.11
Drowsy	14 (60.9%)	9 (39.1%)	6 (26.1%)	9 (39.1%)	
Mildly sedated	9 (39.1%)	14 (60.9%)	17 (73.9%)	14 (60.9%)	
Deeply sedated	0 (0)	0 (0)	0 (0)	0 (0)	
Number of patients needed rescue analgesia					
	7 (30.4%)	3 (13%)	1 (4.3%)	0 (0)	0.008*
Time to first request of analgesics (min)					
	64.78 ± 9.22	98.48 ± 8.97	123.48 ± 7.75	163.04 ± 14.51	0.000*

Data are presented as mean ± SD and frequency (%)

Table 6: Postoperative FLACC scale time and score.

FLACC Score (0 - 10)	Group 1 (n=23)	Group 2 (n=23)	Group 3 (n=23)	Group 4 (n=23)	P value
30 min after surgery					
0 (No pain)	0 (0)	0 (0)	0 (0)	0 (0)	0.000*
1-3 (Mild pain)	0 (0)	16 (69.6%)	20 (87.0%)	23(100%)	
4-6 (Moderate pain)	23 (100%)	7 (30.4%)	3 (13.0%)	0 (0)	
7-10 (Severe pain)	0 (0)	0 (0)	0 (0)	0 (0)	
1 hr after surgery					
0 (No pain)	0 (0)	1 (4.3%)	4 (17.4%)	4 (17.4%)	0.000*
1-3(Mild pain)	14 (60.9%)	21 (91.3%)	19 (82.6%)	19 (82.6%)	
4-6 (Moderate pain)	9 (39.1%)	1 (4.3%)	0 (0)	0 (0)	
7-10 (Severe pain)	0 (0)	0 (0)	0 (0)	0 (0)	
2 hrs after surgery					
0 (No pain)	9 (39.1%)	7 (30.4%)	15 (65.2%)	15 (65.2%)	0.031*
1-3 (Mild pain)	14 (60.9%)	16 (69.6%)	8 (34.8%)	8 (34.8%)	
4 – 6 (Moderate pain)	0 (0)	0 (0)	0 (0)	0 (0)	
7-10 (Severe pain)	0 (0)	0 (0)	0 (0)	0 (0)	
4 hrs after surgery					
0 (No pain)	15 (65.2%)	14 (60.9%)	18 (78.3%)	17 (73.9%)	0.561
1-3 (Mild pain)	8 (34.8%)	9 (39.1%)	5 (21.7%)	6 (26.1%)	
4-6 (Moderate pain)	0 (0)	0 (0)	0 (0)	0 (0)	
7-10 (Severe pain)	0 (0)	0 (0)	0 (0)	0 (0)	

Data are presented as frequency (%)

Table 7: Post-hoc analysis of postoperative FLACC scale among the four groups.

Groups	FLACC after 30 minutes	FLACC after 1 hour	FLACC after 2 hours
Group 1 vs. Group 2	0.000*	0.012*	0.53
Group 1 vs. Group 3	0.000*	0.001*	0.07
Group 1 vs. Group 4	0.000*	0.001*	0.07
Group 2 vs. Group 3	0.15	0.23	0.018*
Group 2 vs. Group 4	0.004*	0.23	0.018*
Group 3 vs. Group 4	0.07	-	-

Discussion

This study was conducted to determine the optimum dose of dexmedetomidine as an adjuvant to intrathecal hyperbaric bupivacaine in infants undergoing infra-umbilical surgeries in Suez Canal University Hospitals. We achieved our study aim through recording and measuring the onset and duration of sensory and motor block, SA technique, need for analgesia, intraoperative sedation, and FLACC scores. The study included 92 patients allocated into 4 groups; with one control group received only intrathecal hyperbaric bupivacaine 0.5% while the other three groups received a different doses of intrathecal dexmedetomidine (0.25, 0.3, 0.4 µg/kg) in addition to hyperbaric bupivacaine 0.5%.

To the best of our knowledge, this is the first study to compare these three different doses of dexmedetomidine in SA among infants. The doses used in our study were extrapolated from adult doses of dexmedetomidine, and would be practically similar to the commonly utilized dose of 5-10 µg in adult patients. Comparison of our results in the current work with similar studies on young populations was not always possible due to the lack of resources that support intrathecal dexmedetomidine in infra-umbilical surgeries in infants. However, several studies are available in adults.

In our study, a 0.3 µg/kg dexmedetomidine in addition to bupivacaine was associated with the best outcomes. This is similar to Fares et al, who compared the analgesic effect of intrathecal fentanyl and dexmedetomidine as adjuvants to bupivacaine in children undergoing surgery for abdominal malignancies. They also found promising results using a comparable dose of 0.2 µg/kg dexmedetomidine like us as an adjuvant to bupivacaine over other agents (9). However, studies that proved good outcomes were linked to higher doses. Tang et al concluded that 5 µg intrathecal dexmedetomidine reduced the median effective dose (ED50) of spinal hyperbaric ropivacaine during cesarean section by approximately 18%. Also, Liu et al found that 5 µg intrathecal dexmedetomidine enhances the efficacy of spinal bupivacaine by 24% in patients undergoing cesarean section with SA (10,11). Moreover, Naaz et al showed that 10 µg of dexmedetomidine was the most optimal intrathecal dose by weighing the prolongation of anesthesia and analgesia and side effects when exploring the optimum dose of dexmedetomidine for intrathecal application in lower abdominal surgery (12).

In our study, the onset of sensory and motor blocks were not statistically significant difference between the 4 studied groups. However, the duration of sensory and motor block had a statistically significant difference between the studied groups, with group 4 significantly higher than other groups. The duration of

sensory block was the least recorded in group 1 (64 minutes), and the longest duration was in group 4 (163 minutes). Similarly, the least duration of motor block was 43 minutes in group 1, and the longest duration was 131 minutes in group 4.

In a recent study by Saha et al who did a prospective comparative randomized double blinded trial on 105 adult patients allocated into 3 equal groups undergoing infra-umbilical surgery under SA. Each group received intrathecal 5, 7.5, and 10 μg of dexmedetomidine added to 15 mg of bupivacaine respectively. They found a statistically significant and dose-dependent shortening of the mean time to peak sensory block (3.9, 3.3, and 2.9 min; $P<0.001$) and peak motor block (5.6, 5.3, and 4.8 min; $P<0.001$) respectively (13).

Also, Shen et al, in a systemic review and meta-analysis, reported that the use of intrathecal dexmedetomidine during cesarean section can shorten the onset time of SA and prolong the sensory and motor block duration (14)**.** Gupta et al also confirmed our findings as they showed that the addition of 10 μg compared with 2.5 μg or 5 μg intrathecal dexmedetomidine to 0.5% hyperbaric bupivacaine was associated with significantly earlier onset of sensory and motor block as well as prolonged duration of sensory and motor block (7)**.**

Similar to our findings, a recent prospective randomized double-blinded placebo controlled trial studied 120 ASA I and II patients undergoing elective cesarean delivery under SA. The patients were randomly allocated into four groups treated with intrathecal ropivacaine 12 mg alone or in combination with dexmedetomidine 5 μg, 7.5 μg and 10 μg. All four groups had no statistically significant onset times of sensory and motor block while dexmedetomidine prolonged the duration of sensory and et al blockade compared to the control group(15)**.** In addition, Singh 2018 performed a prospective comparative randomized study that included 60 ASA class I and II adult patients undergoing infra-umbilical surgeries under SA. The patients were allocated into three groups. Each group received 4, and 8 μg of dexmedetomidine with 3 ml of bupivacaine respectively where no statistically significant difference in the onset of sensory and motor block while there was a significant prolongation in the duration of sensory block and motor block with escalating doses of dexmedetomidine (16)**.**

Moreover, the study of Shaikh and Dattatri 2014 revealed that the mean onset of sensory block was 4.58 minutes with 5 μg of dexmedetomidine (group D1) and 3.57 minutes with 10 μg of dexmedetomidine (Group D2). While, on the other hand, onset of motor block was achieved after 4.70 minutes in group D1 and 4.25 minutes in group D2, which still higher than that in the current study. This depicts two concepts; the first is that higher doses of dexmedetomidine are linked to rapid onset of sensory and motor block, and the second is that the efficacy of dexmedetomidine as an adjuvant is depending on other added drug (17).

It is well known that dexmedetomidine provide excellent sedation during many procedures including cardiac surgeries, upper airway surgeries, minor surgeries, in addition to preparation before imaging such as EEG and MRI (18)**.** This was confirmedin our study; yet, there was no statistically significant difference in level of sedation between the studied groups. In a study by Bong et al, they used dexmedetomidine infusion at the rate of 0.2-1 μg/kg/h for children undergoing inguinal hernia surgeries. They found this dose is highly satisfactory to achieve

sedation with a Ramsay score ranges between 3 and 4 (19).

In our study, the time to first request of analgesia showed that group 4 had a significantly longer duration (163 minutes) than the three other groups, while group 1 was the earliest to need analgesics (64 minutes). Regarding the effect of intrathecal dexmedetomidine on postoperative pain, there were significantly higher FLACC scores after 30 minutes and 1 hour in the group 1 than each of groups 2, 3, and 4 respectively. After 2 hours, the FLACC score was significant higher in group 2 than in groups 3 and 4 respectively.

On the same line, the study of Fares et al who compared the analgesic effect of intrathecal 0.2µg/kg fentanyl and 0.2µg/kg dexmedetomidine as adjuvants to bupivacaine in children undergoing surgery for abdominal malignancy. The first analgesic request was significantly prolonged in dexmedetomidine group (7.67 ± 0.57 hours), in contrast to other groups (5.40 ± 1.09 hours and 4.23 ± 3.27 hours, with $P < 0.04$). In addition, FLACC scores markedly decreased in the fentanyl and dexmedetomidine groups at 6, 8 and 12 hours compared to the control group ($P < 0.05$)(9).

Conclusion

This study produces promising results because it is considered a cornerstone for further research about using dexmedetomidine as an adjuvant in SA in infants and children as a less visited topic. Also, this study compared three different doses of dexmedetomidine in comparison to each other and to control group; that was the first of its kind. However, there were some limitations that we wish further studies could avoid: in infants, the pinprick method of assessing was problematic because it caused discomfort, pain, and restlessness. Additionally, safety and incidence of complications of these different doses of dexmedetomidine should be assessed. Also, various dosages of intrathecal dexmedetomidine as an adjuvant to SA should be compared with intravenous administration in infants undergoing different lower abdominal and orthopedic surgeries.

Conflict of interest

The authors confirmed that this article content has no conflict of interest.

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